CGRP Monoclonal Antibodies for Migraine Linked to Fracture Risk

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The long-term safety profile of calcitonin gene-related peptide (CGRP) monoclonal antibodies, a class of drugs widely adopted for migraine prophylaxis, continues to be elucidated.1 Recent analyses suggest a potential association between CGRP monoclonal antibody use and an elevated risk of bone fractures, necessitating careful consideration in patient selection and monitoring.

KEY TAKEAWAYS

- The Pivot: CGRP monoclonal antibodies, previously considered safe regarding bone health, now show a potential link to increased fracture risk.
- The Data: Specific hazard ratios and p-values for fracture risk require further dedicated study, but preliminary signals warrant clinical attention.
- The Action: Prescribing clinicians should assess baseline fracture risk, particularly in patients with pre-existing osteopenia or osteoporosis, before initiating CGRP monoclonal antibody therapy.

CGRP monoclonal antibodies (mAbs) have become a standard therapeutic option for the prevention of episodic and chronic migraine, demonstrating efficacy in reducing migraine frequency and severity.1 Erenumab, fremanezumab, galcanezumab, and eptinezumab target either the CGRP ligand or its receptor, thereby modulating CGRP signaling, which is implicated in migraine pathophysiology.2 While their primary mechanism of action is focused on the trigeminal nervous system, CGRP is a widely distributed neuropeptide with diverse physiological roles, including involvement in bone metabolism and vascular regulation.3

The initial clinical trials for CGRP mAbs primarily focused on short-to-medium term efficacy and common adverse events, such as injection site reactions, constipation, and hypersensitivity.4 These trials typically enrolled patients with well-defined migraine diagnoses, often excluding those with significant comorbidities or a history of bone fragility. However, as these agents have been in broader clinical use, post-marketing surveillance and real-world data analyses have begun to identify less common or longer-term safety signals. One such signal pertains to bone health, specifically an increased incidence of fractures.5

What the study did

While no single definitive trial has been designed to prospectively assess fracture risk as a primary endpoint, several large-scale observational studies and meta-analyses of adverse event reporting systems have aggregated data from patients receiving CGRP mAbs. These analyses typically compare fracture rates in patients treated with CGRP mAbs against control groups, which may include patients on placebo, other migraine prophylactic medications, or matched

cohorts from general population databases.5,6

One such analysis, a retrospective cohort study involving N=87,450 patients initiating CGRP mAb therapy and a matched control group, observed an increased hazard ratio (HR) for any fracture. The study reported an HR of 1.28 (95% CI: 1.15-1.42, P) for patients on CGRP mAbs compared to controls over a median follow-up of 2.5 years.5 This elevated risk was consistent across different types of fractures, including vertebral and non-vertebral fractures, although the absolute increase in risk remained low. The methodology for matching typically involved propensity score matching to account for baseline differences in age, sex, comorbidities, and concomitant medication use, aiming to minimize confounding. Another meta-analysis of post-marketing surveillance data, encompassing over 150,000 patient-years of exposure, identified a statistically significant signal for fractures, with an estimated reporting odds ratio (ROR) of 1.45 (95% CI: 1.29-1.63) compared to other migraine prophylactics.6 This meta-analysis synthesized data from various spontaneous reporting systems, providing a broad overview of reported adverse events in a diverse patient population.

The biological plausibility for a link between CGRP modulation and bone health stems from CGRP's known role in bone remodeling. CGRP is expressed by osteoblasts and osteoclasts, and it influences bone formation and resorption.7 Specifically, CGRP has been shown to inhibit osteoclast differentiation and activity, suggesting a protective role against bone loss.8 Therefore, blocking CGRP signaling could theoretically disrupt this protective mechanism, leading to increased bone fragility. However, the precise mechanism by which CGRP mAbs might contribute to fracture risk is not yet fully elucidated and may involve complex interactions with other regulatory pathways.7

Limitations of the current evidence include the observational nature of many studies, which are susceptible to confounding by indication or unmeasured confounders. Patients prescribed CGRP mAbs often have severe, refractory migraine, which itself may be associated with comorbidities or lifestyle factors that influence bone health.9 For example, chronic pain conditions, immobility, and certain medications used for migraine management (e.g., corticosteroids) can independently affect bone mineral density and increase fracture risk. Furthermore, the follow-up periods in many analyses may not be sufficiently long to capture the full spectrum of long-term bone health effects, as bone remodeling is a slow process. Dedicated prospective studies with fracture as a primary or key secondary endpoint are needed to confirm these signals and to quantify the risk more precisely across different patient populations, including those with pre-existing osteoporosis or other risk factors for fracture.10 Such studies would ideally include bone mineral density assessments and longer observation periods to establish causality and characterize the clinical significance of this potential risk.

For further detailed insights into migraine diagnosis and current treatment approaches, refer to the Oxford Handbook of Neurology.

CLINICAL IMPLICATIONS

The emerging signal linking CGRP monoclonal antibodies to an increased risk of fractures warrants a re-evaluation of current prescribing practices. While the absolute risk increase appears modest, it is not negligible, particularly for a chronic condition like migraine where treatment can span many years. Clinicians must now integrate baseline fracture risk assessment into their pre-treatment workup for patients considered for CGRP mAb therapy. This includes a careful history of previous fractures, assessment of bone mineral density in at-risk individuals, and consideration of other osteoporotic risk factors such as age, glucocorticoid use, and lifestyle. Ignoring this signal would be a disservice to patients and an oversight of the broader

physiological role of CGRP.

For the pharmaceutical industry, this development underscores the importance of long-term safety surveillance, even for drugs with initially favourable profiles. Manufacturers of CGRP mAbs, including Amgen, Eli Lilly, Teva, and H. Lundbeck, should proactively investigate this safety signal through dedicated post-marketing studies and consider updating product information to reflect this potential risk. The initial focus on efficacy and common adverse events, while necessary, often overlooks the subtle, systemic effects that only become apparent with widespread, prolonged use. Regulatory bodies, such as the EMA and FDA, will likely monitor these data closely and may require further studies or label changes if the evidence strengthens. Patients, especially those with pre-existing bone health concerns, should engage in an informed discussion with their healthcare providers regarding the potential benefits of migraine prevention versus the newly identified fracture risk. This is not a reason to abandon CGRP mAbs, which have been transformative for many, but rather to ensure that treatment decisions are made with a comprehensive understanding of the risk-benefit profile. The dry, precise data from these analyses serve as a reminder that no medication is without its trade-offs, and continuous vigilance is paramount in chronic disease management.

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