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COMMENT

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Situational prevention in migraine: are we doing the right thing?

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Abstract

This commentary addresses the use of rimegepant for situational prevention in migraine management. While the approach of using prophylactic treatments during high-risk periods is not new, its application with rimegepant described by *Lipton et al.* raises ethical and clinical concerns. These include the challenge of defining high-risk periods, the potential for overmedication, and the risk of medication overuse headache (MOH). The current evidence on MOH with gepants is inconclusive, and recommendations on dosing may be insufficient. Additionally, the long-term safety of calcitonin gene-related peptide (CGRP) antagonists remains uncertain, especially regarding cardiovascular and other systemic effects. The commentary emphasizes the need for caution and thorough investigation into the long-term risks and benefits of situational prevention with rimegepant before widespread adoption.

Keywords CGRP, Migraine, Rimegepant, Medication overuse

Every clinician strives to protect patients from potential risks caused by environmental or internal factors that could interfere with the expected results of their prescribed treatment. This principle also applies to migraine management. We read with interest the brief communication by *Lipton et al.* on the potential use of rimegepant for situational prevention, that is treating patients during the interictal phase in situations of increased risk for migraine attacks [1]. While the concept is not entirely new, considering the mini prophylaxis of menstrual migraine with triptans [2], the application of situational prevention to gepants, particularly those with dual therapeutic significance like rimegepant, raises ethical and clinical concerns. Treating asymptomatic individuals purely based on perceived risk periods challenges the ethical principle of "do no harm" and expose patients to unnecessary risks. Defining periods of increased risk for migraine is difficult as they vary widely among patients, occurring as infrequently as once a year or as often as twice per week. The brief communication suggests that situational prevention could be applied to various conditions, including stressful life events, weekends, time zone changes due to flights, and other triggers. The lack of a clear definition for these periods places the decision to take the drug entirely in the hands of patients, significantly increasing the risk of near-daily intake and consequent overmedication. Excessive medication use poses challenges in migraine patients, such as the development of medication-overuse headache (MOH). While patient education is an essential component in mitigating the risk of medication overuse, it alone cannot fully prevent inappropriate use of rimegepant for situational prevention. Variability in patient understanding and the unpredictable nature of migraine triggers lead to challenges in adherence to recommended dosing schedules. Patients often underestimate the risks asso-

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ciated with frequent use, particularly if immediate side effects are not apparent. They might perceive situational prevention as a more convenient and proactive approach, potentially leading to overuse. The theoretical risk of MOH with gepants has been questioned [3], but we have no evidence that MOH does not arise in the medium-long term, beyond the 52 weeks monitored in randomized controlled trials [4]. The recommendation to not exceed 18 doses per month may be inadequate, as MOH could develop before this threshold is reached. Evidence from other migraine therapies, such as triptans (limited to 10 doses per month) and nonsteroidal anti-inflammatory drugs (limited to 15 doses per month), demonstrates that even less frequent usage can lead to MOH, a biological disorder characterized by structural changes in the brain [5]. The three individual cases presented in this communication are not representative of the entire migraine population, many of whom are already on a prophylactic regimen, possibly involving another calcitonin gene-related peptide (CGRP) inhibitor. These cases involve only a few doses of rimegepant: two patients tried situational prevention twice, while the third patient tried it only once. Positive expectations from this therapy have likely played a role, and the observed positive effects may have been driven solely by placebo. Moreover, the prolonged antagonism of the CGRP pathway has unforeseen consequences [6]. Clinical trials of rimegepant have excluded patients with uncontrolled, unstable, or recently diagnosed cardiovascular disease, poorly controlled hypertension, and individuals with a recent history of stroke or myocardial infarction. In mice, rimegepant worsened ischemic stroke, diminished collateral flow and reduced reperfusion success [7]. In humans, post-marketing data and a prospective study with erenumab, a monoclonal antibody targeting the CGRP receptor, have indicated a risk of elevated blood pressure and related complications [8, 9]. These concerns have led to a warning about hypertension being added to the package leaflet of erenumab. While rimegepant is a small-molecule antagonist of the CGRP receptor with a similar mechanism of action to erenumab, we currently lack data on its long-term consequences. CGRP plays a further role in physiological functions across different systems, including the central nervous, gastrointestinal, and reproductive ones. The risk of hepatotoxicity has been ruled out for rimegepant in the short term [10, 11], but the possibility of hepatotoxicity re-emerging as an adverse event with long-term use remains a concern. In a phase 2/3 trial where rimegepant was administered every other day for 12 weeks, some subjects experienced elevations in liver enzymes, indicating potential liver stress [12]. The long-term effects of CGRP antagonists on other systems remain unknown, with much of the research to date conducted in animal models that do not always correlate with human outcomes. The subliminal message conveyed by this communication could be seen not only as a stimulus for controlled and in-depth studies on mini prophylaxis, now referred to as situational prevention, but also as a potential license for the too casual use of rimegepant. In medicine, caution is paramount, especially given the current lack of long-term studies for rimegepant, making it difficult to advocate for its ongoing use without fully understanding the long-term safety profile [13]. We hope that the scientific community will prioritize studies to elucidate the need of risks of potential adverse effects of any gepant before evaluating the need of placebo-controlled trials to assess the efficacy and safety of situational prevention.

Abbreviations

CGRP calcitonin gene-related peptide
MOH medication overuse headache

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

Lanfranco Pellesi serves as member of Editorial Board of European Journal of Medical Research and Junior Editorial Board of The Journal of Headache and Pain. Paolo Martelletti serves as Editor in Chief of The Journal of Headache and Pain, Editor in Chief of SN Comprehensive Clinical Medicine, Member of Editorial Board of Internal and Emergency Medicine, Pain & Therapy, Expert Review of Neurotherapeutics, Neurology & Therapy, and Expert Member of European Medicines Agency.

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