Gefapixant for Refractory or Unexplained Chronic Cough?

Richard S. Irwin, MD; J. Mark Madison, MD

In this issue of JAMA, Kum and colleagues report the results of a high-quality systematic review and dose-response meta-analysis that evaluated the efficacy and tolerability of gefapixant for the treatment of adults with refractory or unexplained chronic cough. Gefapixant, a P2X3 receptor antagonist that blocks the adenosine triphosphate–gated ion channel on chemically sensitive airway C-fibers, has the potential to decrease cough by reducing activation of airway C-fibers that transmit action potentials to the brain.\(^1\)\(^-\)\(^4\) Kum et al\(^1\) rated their certainty as to whether patients would perceive the treatment effects as important by comparing their results with the minimal important difference (MID) of the outcome measures that have been reported in the literature\(^5\)\(^-\)\(^7\) as well as by surveying a small number (n = 5) of their own patients with refractory or unexplained chronic coughs for MIDs related to adverse effects. The MID is the smallest difference in scores of an outcome measure perceived by patients as beneficial or harmful and which would lead a clinician to consider a change in treatment.\(^8\)

From an extensive search, Kum et al\(^1\) identified 11 eligible randomized clinical trials enrolling 3027 patients with typical characteristics of adults with chronic cough between November 2014 and July 2023. Nine trials including 2980 patients (median duration of cough, 11.6 years) were included in the primary analysis. Adequate data were available to assess results for the effects of dose ranges of gefapixant (twice-daily dosing of 15, 30, 45, and 60 mg) and placebo on 24-hour and awake cough frequency, cough severity, cough quality of life, and treatment-related adverse events. Compared with placebo, while the 15-mg dosing was associated with a small and insignificant improvement in cough, it was associated with the fewest adverse occurrences. Even though the 60-mg dosing led to the most cough improvement, it was the least tolerable. These are the reasons why the largest phase 3 randomized clinical trials—eg, COUGH-1 and COUGH-2—were designed to study twice-daily gefapixant doses of 15 and 45 mg.\(^9\)

Kum et al\(^1\) primarily analyzed dosing at 45 mg twice daily because they reasonably considered that regulators in countries where the drug is still being considered for approval would most likely focus on the 45-mg dose.\(^1\) Compared with placebo, a twice-daily gefapixant dose of 45 mg had only small effects on 24-hour cough frequency (16.0% reduction), awake cough frequency (17.6% reduction), cough severity (6.2-mm reduction on a 100-mm visual analog scale), and cough quality of life on the Leicester Cough Questionnaire (LCQ) (1.0-point improvement) but much larger treatment-related (absolute 32% increase) and taste-related (absolute 32% increase) adverse events.

The meta-analysis of Kum et al\(^1\) aligns closely with the results of the phase 3 COUGH-1 and COUGH-2 gefapixant trials but has greater precision.\(^9\) Compared with MIDs of 20% for reduction of cough frequency, 30 mm for reduction for cough severity, and 1.3 points for improvement in quality of life on the LCQ, none of the small improvements in cough (compared with placebo) detected by Kum et al\(^1\) would likely be perceived by patients as clinically important. On the other hand, by surveying their 5 patients with refractory or unexplained chronic coughs, Kum et al\(^1\) were able to estimate MIDs for treatment-related adverse events at 15% and taste-related adverse events at 10%; that is, these 5 patients would very likely find the adverse effects of 45-mg dosing of gefapixant to not be worth the small improvements in cough. Therefore, based on the analyses of Kum et al\(^1\), gefapixant does not appear to have satisfied the unmet need for successfully treating patients with chronic refractory or unexplained coughs with an efficacious and tolerable drug.

Although gefapixant did appear to have a small effect on improving cough compared with placebo, the effects were marginal when compared with the large, favorable effects of placebo alone. In the placebo group, Kum et al\(^1\) identified substantial mean improvements from baseline in awake cough frequency (54.8%), cough severity on the visual analog scale (24.2 mm), and cough quality of life on the LCQ (3.0 points).

Why should patients with a truly chronic refractory and unexplained cough consistently respond so favorably to mere placebo and do so for 12 weeks in COUGH-1 and 24 weeks in COUGH-2\(^1\) and then for 52 weeks in blinded extension periods of 40 weeks in COUGH-1 and 28 weeks in COUGH-2\(^1\)? The most likely explanation is that it is due to the importance of the placebo effect in cough clinical trials, a phenomenon that has been known for years primarily in acute cough studies\(^1\)\(^1\) but one that is especially prominent in the gefapixant trials. Kum et al\(^1\) nicely summarize what researchers have speculated about the potential reasons for the placebo responses. These include that participating in trials favorably alters expectations of participants, which may lead to release of endogenous opioids; the possibility of investigator enthusiasm influencing patient expectations; natural disease course; regression to the mean (ie, following an extreme random event, the next random event is likely to be less extreme); and/or activation of the Hawthorne effect (ie, individuals modifying behavior in response to awareness of being observed). Also, it would not be surprising if study participants with taste-related adverse effects suspected that they were receiving the active drug, effectively unblinding some participants. Whatever the reason(s) for the large placebo effect, it is important to compare any new drug with placebo; it is the only way to control for the placebo effect of the trial drug and estimate the true, specific, drug effect.\(^1\)\(^2\)
It is possible that the placebo group improved so much, and did so consistently for a full year, because many of the patients did not have a truly refractory or unexplained chronic cough. We ask this because the clinical literature, and our own experience, has not documented the existence of patients with truly refractory or truly unexplained chronic cough who respond so favorably to any type of treatment—let alone placebo—for an entire year. While it is not possible for us to know the answer to our question, certain features of the COUGH-1 and COUGH-2 trials suggest that our question is relevant. For instance, patients were screened in March of 2018 for COUGH-1 and COUGH-2 but were worked up according to the older CHEST 2006 cough guidelines but had been updated well before enrollment had started. Those updates, based on progress since 2006, aimed (1) to address the concern about lack of intervention fidelity to recommendations since 2006, aimed (1) to address the concern about lack of intervention fidelity to recommend

### ARTICLE INFORMATION

**Author Affiliations:** Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Massachusetts Chan Medical School, Worcester.

**Corresponding Author:** Richard S. Irwin, MD, Division of Pulmonary, Allergy, and Critical Care Medicine, 55 Lake Ave N, Worcester, MA 01655 (Richard.Irwin@umassmemorial.org).

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**Conflict of Interest Disclosures:** Dr Irwin reported that he is a codetector of the Pnum Ladder, a cough severity and cough quality of life visual analog scale; that he is a codeveloper and co-copyright holder of the Cough Quality-of-Life Questionnaire (CQLQ); and that he is chair of the CHEST cough expert panel. Dr Madison reported that he is a member of the CHEST cough expert panel. Dr Irwin is a codeveloper and co-copyright holder of the Cough Quality-of-Life Questionnaire (CQLQ); and that he is chair of the CHEST cough expert panel. Dr Madison reported that he is a member of the CHEST cough expert panel.

**REFERENCES**


