Camlipixant: A New Treatment Option for Refractory Chronic Cough?

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Treatments for chronic refractory cough that act centrally are not particularly effective and are often accompanied by adverse effects. A number of medications targeting purinergic receptors in vagal afferent nerves have recently been under investigation. One of them, gefapixant, has been approved for use in Japan and Switzerland. However, it has not been approved by the US Food and Drug Administration or the European Medicines Agency yet. Camlipixant, another drug in this class, is currently being studied in a phase III trial.

Keywords

Chronic cough, camlipixant, gefapixant, purinergic receptor antagonists, refractory chronic cough, vagal afferent nerves

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Chronic cough is a cough that lasts 8 weeks or longer and is not due to serious underlying conditions. It is a common problem in primary care, accounting for up to 40% of referrals to pulmonologists.[1] Common causes include rhinosinusitis, cough-variant asthma, eosinophilic bronchitis, smoking, certain medications (including angiotensin-converting enzyme inhibitors) and gastroesophageal reflux.[2]

Once serious underlying conditions have been excluded, patients with chronic cough should be treated empirically for the suspected cause. Early reports suggest that this approach is successful in virtually all cases.[2] Straightforward cases of chronic cough are managed in primary care, with a success rate of approximately 70% among the more challenging cases referred to chronic cough clinics.[3] The remaining 30% of cases are labelled as refractory chronic cough (RCC) when it fails to respond to therapy or unexplained chronic cough (UCC) when the aetiology is unclear.

Refractory and unexplained chronic cough

RCC and UCC have parallel features to neuropathic pain. Patients with neuropathic pain experience paraesthesia, hyperalgesia and allodynia. Patients with RCC or UCC experience laryngeal paraesthesia, an itch or tickling sensation in the back of the throat; hypertussia, an exaggerated response to mild cough stimuli; and allotussia, a cough from non-cough stimuli, such as talking or laughing.[1]

Moreover, differences in the central and peripheral nervous system have been reported between patients with chronic cough and patients without chronic cough. Magnetic resonance imaging findings have shown differences in activity in some parts of the brain of patients with chronic cough compared with those not suffering from this condition.[4] In particular, the anterior cingulate cortex, an area involved in cough suppression, is smaller in patients with chronic cough than in patients without chronic cough.[4] Bronchial biopsies from patients with chronic cough with normal pulmonary function and chest imaging have shown greater nerve density in the bronchial epithelium than in control subjects.[5]

Treatment of refractory and unexplained chronic cough

The treatment of cases of RCC and UCC is challenging. A speech pathology approach, which uses techniques similar to those used to treat hyperfunctional voice disorders and vocal cord dysfunction, is successful in approximately half of the cases.[6,7] The pharmacologic treatment of these conditions is challenging. The last drug approved for the treatment of cough was dextromethorphan in 1958, and it is not particularly effective.[8]

Since there are parallels between the two conditions, drugs used for neuropathic pain have been used in patients with chronic cough. Subjective outcomes, such as cough-specific quality of life, as measured by the Leicester Cough Questionnaire (LCQ), and subjective cough severity improved; however, objective improvements have not been reported with low-dose morphine, amitriptyline or pregabalin.[1,9–11] One small randomized trial with gabapentin reported a reduction in cough frequency.[11] However, it had several limitations: it was a very small study, the placebo group had a much higher baseline cough frequency, and cough frequency was only monitored for

1 hour on study visit days.[11] Side effects from these medications include gastrointestinal upset and drowsiness.

Orvepitant is a centrally acting neurokinin antagonist that failed to improve chronic cough.[12] The American College of Chest Physicians suggests the use of speech pathology therapy techniques and gabapentin for the treatment of RCC and UCC.[13] The literature search for the guideline was completed before the pregabalin report was published, but it probably would also have been included as an option in the guideline. The European Respiratory Society chronic cough guidelines also recommend trials of morphine, gabapentin or pregabalin in RCC.[14]

The role of vagal afferent nerves in chronic cough

Afferent vagal nerve fibres carry urge-to-cough signals to the cough centres in the brainstem. There are two types of fibres: Aδ fibres are thinly myelinated nerve fibres that serve as mechanoreceptors responding to the presence of particles, mucus and changes in pH or osmolarity in the airways, and C fibres are nonmyelinated nerve fibres that are normally inactive in healthy airways. C fibres contain receptors that respond to a variety of stimuli, including smoke, air pollution, allicin and capsaicin.[15]

The antagonists developed for these receptors have not improved chronic cough. An antagonist to transient receptor potential vanilloid (TRPV) 1, a type of receptor found on vagal afferent nerves, reduced capsaicin-induced cough but did not decrease spontaneous awake cough frequency in patients with RCC.[16] Another study also did not find another TRPV1 receptor antagonist to improve RCC.[17]

Purinergic receptor antagonists

Cell injury releases adenosine triphosphate (ATP), and C fibres also contain purinergic P2X3 receptors.[18] Clinical trials investigating two of the receptor antagonists in this class of molecules have been terminated. Eliapixant was found to cause hepatotoxicity,[19] and the phase IIb trial investigating sivopixant was disappointing (ClinicalTrials.gov identifier NCT04110054).[20]

Phase III trials with a third molecule in this class, gefapixant, have been completed.[21] Reports of its effects at 12, 24 and 52 weeks have been published.[21,22] A dose of 45 mg (but not 15 mg) twice daily resulted in a statistically significant improvement in cough frequency, cough severity and cough-specific quality of life as measured by the LCQ. However, these improvements did not reach the minimum clinically important difference for any of these parameters.[23,24] Moreover, dysgeusia was reported by most patients treated with gefapixant, and study discontinuations were twice as common with patients treated with gefapixant than with participants treated with placebo.[21,22] In 2022, the US Food and Drug Administration decided not to approve gefapixant[25] ; however, it has been approved in Japan and Switzerland under the trade name Lyfnua® (Merck & Co., Kenilworth, NJ, USA).[26] The European Medicines Agency recently released the following statement: "On July 20, 2023 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product, Lyfnua intended for the treatment of refractory or unexplained chronic cough".[27] The recommended dose is 45 mg twice daily.[27]

The P2X3 receptor is a trimer comprising either three identical P2X3 subunits or two P2X3 and one P2X2 subunits (P2X2/3). Animal studies have indicated that P2X2/3 receptors play an important role in taste perception, and it has been suggested that the taste disturbances with gefapixant may be due to its modest selectivity for P2X3 compared with P2X3/2 receptors.[24] Sivopixant is a selective P2X3 receptor antagonist. Unfortunately, the phase IIb study with this molecule was disappointing.[20] None of the three doses trialled improved cough frequency, cough severity or cough-specific quality of life as measured by the LCQ compared with placebo.[18]

Camlipixant

Camlipixant is a selective P2X3 antagonist undergoing development.[28] Only one of the 24 normal subjects in the phase I trial complained of any taste alteration. Recruitment for the phase IIa trial dose escalation trial was disrupted by the coronavirus disease 2019 pandemic. None of the doses trialled reduced awake cough frequency compared with placebo. However, post hoc analyses have demonstrated that camlipixant is effective in individuals who average 25 or more coughs/hour.[29] As of 2 August 2023, results from the phase IIb study have only been published in an abstract.[30] The phase IIb trial limited recruitment to individuals with 20 or more coughs/hour and those rating cough severity of at least 40 mm on a 100 mm visual analogue scale. Approximately 250 participants were randomized to receive 12.5 mg, 50 mg, 200 mg or placebo twice daily for 4 weeks. Those receiving 50 mg or 200 mg twice daily had a 34% greater reduction in cough frequency than the placebo group.[27] More patients receiving camlipixant experienced an improvement in subjective cough severity than patients receiving placebo.[30] Approximately 5% of patients on any of the three camlipixant doses experienced dysgeusia. The reduction in cough frequency was not affected by the presence of dysgeusia.[31] A phase III study comparing 25 mg and 50 mg twice daily with placebo over 52 weeks is underway.

If the phase III trial with 50 mg twice daily camlipixant duplicates the results of the phase IIb trial (i.e. reducing cough frequency by 30% or more with only a small number of participants experiencing dysgeusia and no other serious adverse effects), camlipixant will likely be approved by the drug regulatory agencies. This approval will represent a major advance in the treatment of patients with RCC or UCC. However, the drug has not been shown to be effective in patients with fewer than 25 coughs/hour and in those who rate their cough severity as less than 40 mm on a 100 mm visual analogue scale. Unless further studies show a benefit in patients with less frequent and less severe coughs, approval for its use should be limited to those who meet these criteria. ❑

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