

coronavirus disease (COVID-19) (6). This relationship, however, is not guaranteed. It is possible, as noted by Scott and colleagues, that an intervention's mechanism of action might provide greater benefit to patients at a lower risk (7), in which case what is gained by increasing the event rate may be lost through a lower treatment effect in the selected population. In addition, the results (regarding either efficacy or safety) of a trial conducted in a prognostically enriched population may not translate to the patients at a lower risk; the benefit/risk tradeoff might be substantially different. If, for example, the percentage of patients who experience a severe side effect is fixed at 0.5% and the drug's benefit leads to a relative risk of 50%, then the risk/benefit tradeoff will be more favorable in a high-risk population, in which event rates might drop from 10% to 5%, than in a low-risk group, in which event rates might drop from 0.2% to 0.1%.

The current COVID-19 pandemic, during which new, rapidly developed, and high-quality evidence is desperately needed to inform medical decision making, has highlighted for the broader public what clinical trialists have known for decades: a multitude of difficult decisions must be made when designing and conducting a clinical trial, with numerous important tradeoffs being considered. Investigators who design PAH trials, and likely those studying many other conditions, are now better informed about the potential benefits of prognostic enrichment thanks to the work presented by Scott and colleagues (3). We hope and expect their study to not only inform the design of PAH trials but to also prompt additional research that will inform and advance clinical trial design in the future. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Kert Viele, Ph.D.
Berry Consultants
Austin, Texas

Timothy D. Girard, M.D., M.S.C.I.
Department of Critical Care Medicine
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

ORCID ID: 0000-0002-9833-4871 (T.D.G.).

References

1. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Enrichment strategies for clinical trials to support determination of effectiveness of human drugs and biological products: guidance for industry. Silver Spring, MD: Food and Drug Administration; 2019 [accessed 2020 Sep 18]. Available from: <https://www.fda.gov/media/121320/download>.
2. Temple R. Enrichment of clinical study populations. *Clin Pharmacol Ther* 2010;88:774–778.
3. Scott JV, Garnett CE, Kanwar MK, Stockbridge NL, Benza RL. Enrichment benefits of risk algorithms for pulmonary arterial hypertension clinical trials. *Am J Respir Crit Care Med* 2021;203:726–736.
4. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429–1435.
5. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest* 2019;156:323–337.
6. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L; et al. Recovery Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med* [online ahead of print] 17 Jul 2020; DOI: 10.1056/NEJMoa2021436.
7. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med* 2020;383:1813–1826.

Copyright © 2021 by the American Thoracic Society



⊗ Neurokinin-1 Receptor Inhibition and Cough

There is a need for better treatment for cough. Unexplained or chronic refractory cough (CRC) is the focus of several recent and ongoing large drug trials, with particular interest in antagonists of ATP-stimulated P2X receptors (1). Although such drugs appear very promising, there are nonresponders, and side effects may be unacceptable to some (2). Hence, a requirement for alternative approaches, not only for CRC but also for cough associated with chronic and incurable diseases of the lung, such as lung cancer, is needed. In this issue of the *Journal*, Smith and colleagues (pp. 737–745) present their findings on aprepitant for cough in

non-radically treatable lung cancer, which, considering the current need, are very welcome (3).

Aprepitant is an antagonist of NK1 (neurokinin 1), a G protein-coupled receptor triggered by the ligand Substance P (SP). NK1 receptors are present in the central and peripheral nervous system as well in other tissues, with apparently varied physiological functions (4). Of note is the possible involvement of SP in sensory disorders, including overactive bladder and chronic itch (5). An important role of NK1 in cough has also been postulated. Within the nucleus tractus solitarius in the brain stem, there have been repeated observations in animal models of the activity of SP and NK1 inhibition on the cough reflex (6). Vagal afferent C fibers in the airway appear to produce SP, and selective NK1 antagonism specifically blocks C fiber-dependent coughing in guinea pigs (7). In humans with respiratory disease, inhaled SP can induce cough (8).

Previous trials of NK1 antagonists in humans with airway disease have failed to impact cough. The selective antagonist CP-99,994 did not demonstrate an effect in 14 subjects with mild asthma on hypertonic

⊗ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202010-3783ED on October 27, 2020

saline-induced numbers of coughs or bronchoconstriction (9). However, this may relate to minimal pathologic cough in the study subjects or to the selection of an inappropriate trial endpoint; experimentally induced cough correlates poorly with daily cough frequency (10). The NK1/2 inhibitor DNK333 apparently failed to demonstrate efficacy on self-reported cough over 2 weeks in 28 individuals with chronic obstructive pulmonary disease, although these findings are not fully reported (11).

Aprepitant is a member of the class that probably has more central nervous system penetration than other NK1 inhibitors. The drug is licensed in the United Kingdom as an antiemetic in patients receiving systemic anticancer therapy, likely acting centrally. Patients with lung cancer are therefore a logical group in whom to explore potential antitussive effects. Smith and colleagues' study participants were a real-world sample of patients from a UK lung oncology clinic who were bothered by cough (3). The group was mixed, with either small cell or stage 3–4 non-small-cell lung cancer of several histological subtypes. Tumors were either peripherally or centrally located (the latter presumably being more likely to produce airway-related symptoms). Current smokers were included, as were patients receiving drugs known to impact cough, including opiates, gabapentin, and ACE inhibitors (albeit at an established and fixed regular dose). Coexisting lung diseases or other relevant pathologic conditions such as acid reflux were not excluded. The particular underlying triggers to cough were therefore likely varied in this heterogeneous group.

In a randomized double-blinded crossover study design, 20 patients received either aprepitant for 3 days (at the standard antiemetic dosing of 125 mg and then 80 mg once daily) followed by placebo for another 3 days, or *vice versa*, with a 3-day washout period in between. Change in cough frequency during waking hours was the primary endpoint, measured with a portable acoustic cough monitor for 24 hours at baseline and on Day 3 of each treatment. Patient-reported symptom scores were the main secondary outcome.

A significant reduction of 22% in mean awake cough frequency was observed with the drug compared with placebo. There were also significant and clinically meaningful average improvements in all three subjectively reported measures of cough. No significant adverse events were associated with the study drug.

These results are very encouraging and have formed part of a renewed interest in NK1 inhibitors in cough. However, this is clearly a small pilot study in a mixed group. As well as showing the interindividual differences between subjects at baseline, Figure 3 in the paper by Smith and colleagues demonstrates the large heterogeneity in outcomes (3). Awake cough frequency in perhaps half of participants was either very similar or higher after receiving aprepitant than after receiving placebo (Figure 3A in Reference 3). Some of this similarity could potentially relate to inadequate washout between treatments in the participants who were randomized to the study drug first; cough frequency measurement was not repeated between the end of treatment 1 and the start of treatment 2. Only larger studies of longer duration will cast light on the interactions between potential antitussive effects of aprepitant and individual triggers and determinants of coughing. Furthermore, doses higher than those used in this trial may lead to more than the modest overall reductions in cough counts reported here.

Evidence for the efficacy of NK1 inhibitors for cough in patients with conditions other than lung cancer is so far very limited,

although there are recent data. In an open-label study of 13 patients with CRC, orvepitant at 30 mg once daily for 4 weeks was associated with a 26% reduction in cough frequency (12). With three different doses, preliminary reports from the phase 2b randomized controlled trial VOLCANO-2 (A Double-Blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Three Doses of Orvepitant in Subjects with Chronic Refractory Cough) are of a failure to demonstrate overall efficacy of orvepitant on cough frequency in CRC. However, in a prespecified analysis, there was a trend for reductions in cough counts in those with higher cough frequencies. Furthermore, across all subjects, there were significant improvements in patient-related outcomes with the higher dose (30 mg once daily) and, again, no significant adverse events compared with placebo (13). Meanwhile, a randomized controlled trial of serlopitant at 5 mg once daily has failed to demonstrate any effect on cough frequency or symptoms in CRC (14). Whether higher doses of both drugs would have achieved different outcomes is not clear; full NK1 receptor blockade may be required for clinical efficacy (15).

In terms of potential mechanisms of action of aprepitant in cough, these are explored in the second part of Smith and colleagues' study (3). SP applied to tissue samples of the vagus nerve from both guinea pigs and humans induced depolarization, a response that was specifically inhibited by exposure of the samples to aprepitant. This raises the possibility of important peripheral antitussive sites of action of NK1 inhibitors in the airway as well as, or instead of, at the level of the brainstem. There could therefore be an analogy with the suggested significant role of SP and NK1 in itch signaling, in this case all along the pathway from sensory afferents (including C fibers), to dorsal horn cells, ascending sensory spinal neurons and higher centers (5). The current study has demonstrated that there is still a lot to learn about NK1 antagonists, which may still yet have potential as much-needed novel treatments for cough. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Richard D. Turner, Ph.D.
Department of Respiratory Medicine
Imperial College Healthcare National Health Service Trust
London, United Kingdom

Surinder S. Biring, M.D.
School of Basic and Medical Biosciences
King's College London
London, United Kingdom

ORCID ID: 0000-0002-3024-6971 (R.D.T.).

References

- Turner RD, Biring SS. Chronic cough: ATP, afferent pathways and hypersensitivity. *Eur Respir J* 2019;54:1900889.
- Smith JA, Kitt MM, Morice AH, Biring SS, McGarvey LP, Sher MR, *et al.*; Protocol 012 Investigators. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. *Lancet Respir Med* 2020;8:775–785.
- Smith JA, Harle A, Dockry R, Holt K, Russell P, Molassiotis A, *et al.* Aprepitant for cough in lung cancer: a randomized placebo-controlled trial and mechanistic insights. *Am J Respir Crit Care Med* 2021;203:737–745.

4. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev* 2014;94:265–301.
5. Ständer S, Yosipovitch G. Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus. *Br J Dermatol* 2019; 181:932–938.
6. Mutolo D, Bongiani F, Fontana GA, Pantaleo T. The role of excitatory amino acids and Substance P in the mediation of the cough reflex within the nucleus tractus solitarius of the rabbit. *Brain Res Bull* 2007;74: 284–293.
7. Mazzone SB, Mori N, Canning BJ. Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. *J Physiol* 2005;569:559–573.
8. Hope-Gill BDM, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:995–1002.
9. Fahy JV, Wong HH, Geppetti P, Reis JM, Harris SC, Maclean DB, et al. Effect of an NK1 receptor antagonist (CP-99,994) on hypertonic saline-induced bronchoconstriction and cough in male asthmatic subjects. *Am J Respir Crit Care Med* 1995;152:879–884.
10. Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *J Allergy Clin Immunol* 2014;134:56–62.
11. Pascoe S, Knight H, Chung K. DNK333 a dual NK1/NK2 receptor antagonist does not inhibit cough in COPD [abstract]. *Am J Respir Crit Care Med* 2007;175:A451. [Published retraction appears in *Am J Respir Crit Care Med* 2011;183:418].
12. Smith J, Allman D, Badri H, Miller R, Morris J, Satia I, et al. The neurokinin-1 receptor antagonist orvepitant is a novel antitussive therapy for chronic refractory cough: results from a phase 2 pilot study (VOLCANO-1). *Chest* 2020;157:111–118.
13. Smith J, Ballantyne E, Kerr M, Mcgarvey L, Morice A, Sher M, et al. Late breaking abstract: the neurokinin-1 receptor antagonist orvepitant improves chronic cough symptoms—results from a phase 2b trial [abstract]. *Eur Respir J* 2019;54:PA600.
14. Menlo Therapeutics Inc. Study of the efficacy, safety, and tolerability of serlopitant for the treatment of refractory chronic cough. Bethesda, MD: U.S. National Library of Medicine, NIH; 2020 [accessed 2020 Sep 27]. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT03282591>.
15. Ratti E, Bettica P, Alexander R, Archer G, Carpenter D, Evoniuk G, et al. Full central neurokinin-1 receptor blockade is required for efficacy in depression: evidence from orvepitant clinical studies. *J Psychopharmacol* 2013;27:424–434.

Copyright © 2021 by the American Thoracic Society



Endotyping in Patients with Obstructive Sleep Apnea and Hypoglossal Nerve Stimulation

The Golden Goal to a Successful Treatment?

In this issue of the *Journal*, Op de Beek and colleagues (pp. 746–755) report about the different endotypes in patients with obstructive sleep apnea (OSA) and which of these factors have influence on outcomes for hypoglossal nerve stimulation (HGNS) (1). The authors' tremendous work will help future patient selection to be more precise regarding various treatment options. HGNS for patients who are noncompliant with the standard treatment of continuous positive airway pressure (CPAP) therapy has rapidly emerged in the foundational clinical routine in Western industrialized countries (2, 3). Nonetheless, approximately one-third of the patients are incomplete responders, fueling the need for more discerning selection criteria. Op de Beek and colleagues used polysomnographic data from the STAR trial to assess the pathophysiological mechanisms, namely, arousal threshold, loop gain, collapsibility, and muscle compensation (4). The authors demonstrated that all four key traits were associated with clinical outcomes in HGNS therapy. Somewhat paradoxically, collapsibility was more severe in responders versus nonresponders and arousal threshold higher in patients who responded to HGNS therapy. These results are striking and provide novel insights into the mechanism of HGNS in patients with OSA. Most notably, a high arousal threshold showed a significantly

favorable effect on outcomes, which is really surprising, because one would normally expect that a higher arousal threshold is associated with poorer sleep quality and that patients who receive HGNS would complain more about disturbing stimulations during sleep at night. The authors found that a higher arousal threshold at baseline corresponded with a larger therapeutic window for HGNS. However, a plausible, mechanistic explanation of this phenomenon remains elusive. Regarding the critical closing pressure (Pcrit), another interesting point arose. Measuring Pcrit is the gold standard to measure the pharyngeal airway collapsibility (5). As Pcrit increases, the more collapsible the upper airway seems to be. In clinical trials, the Pcrit was associated with therapeutic CPAP pressures (6). Patients with modest collapsibility of the upper airway (lower Pcrit) had a lower therapeutic CPAP level (7). One would also expect that patients with a lower Pcrit would be easier to treat with HGNS. The reverse was, in fact, true. Op de Beek and colleagues explain this phenomenon by elucidating that lower pharyngeal collapsibility is associated with more nonanatomical deficits underlying the OSA etiology (high loop gain, low arousal threshold). Although compelling, the relatively modest number of patients with severe collapsibility available for this analysis was too low to draw conclusions, and further clinical trials are merited.

Next, a higher loop gain was associated with lower HGNS response, which makes sense, in that a more severe loop gain indicates a more central-OSA phenotype (8). Anatomical factors, which are contributing to OSA in patients with HGNS therapy, are easier to treat versus attempts to solve a hypersensitive ventilatory control.

Ⓒ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202010-3897ED on November 10, 2020