Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: A double-blind randomized controlled trial

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Background: Inhalation of capsaicin, the extract of hot chili peppers, induces coughing in both animals and human subjects through activation of transient receptor potential vanilloid 1 (TRPV1) on airway sensory nerves. Therefore the TRPV1 receptor is an attractive target for the development of antitussive agents.

Objective: We sought to assess the antitussive effect of TRPV1 antagonism in patients with refractory chronic cough.

Methods: Twenty-one subjects with refractory chronic cough (>8 weeks) attending a specialist clinic were recruited to a randomized, double-blind, placebo-controlled crossover trial assessing a TRPV1 antagonist (SB-705498). Cough reflex sensitivity to capsaicin (concentration of capsaicin inducing at least 5 coughs) and 24-hour cough frequency were coprimary end points assessed after a single dose of SB-705498 (600 mg) and matched placebo. Cough severity and urge to cough were reported on visual analog scales, and cough-specific quality of life data were also collected.

Results: Treatment with SB-705498 produced a significant improvement in cough reflex sensitivity to capsaicin at 2 hours and a borderline significant improvement at 24 hours compared with placebo (adjusted mean difference of +1.3 doubling doses at 2 hours [95% CI, +0.3 to +2.2; $P = .0049$] and +0.7 doubling doses at 24 hours [95% CI, +0.0 to +1.5; $P = .0259$]). However, 24-hour objective cough frequency was not improved compared with placebo. Patient-reported cough severity, urge to cough, and cough-specific quality of life similarly suggested no effect of SB-705498.

Conclusion: This study raises important questions about both the role of TRVP1-mediated mechanisms in patients with refractory chronic cough and also the predictive value of capsaicin challenge testing in the assessment of novel antitussive agents. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Cough, transient receptor potential vanilloid 1, capsaicin, cough sounds, sensory nerves*

Effective antitussive agents remain a significant unmet clinical need. It has been known for decades that inhaling aerosols of the hot chili pepper extract, capsaicin, induces coughing.[1-3] Furthermore, clinical studies have demonstrated that patients with chronic dry cough have heightened responses to inhaled capsaicin[4-8] that improve with successful treatment.[9] Consequently, capsaicin challenge has become an established tool in cough research,[10] and the receptor responsible for transducing capsaicin responses, the transient receptor potential vanilloid 1 (TRPV1), is an attractive target for the development of antitussive agents.

First described in 1997,[11] TRPV1 is primarily expressed by unmyelinated sensory nerves (C-fibers)[12,13] and, in addition to cough, is responsible for the burning pain associated with capsaicin exposure. It is a polymodal transducer, activated not only through vanilloids like capsaicin but also through a wide variety of other stimuli, such as heat,[11] acidity,[14] inflammatory mediators (bradykinin, prostaglandin E_2, and leukotriene B_4),[15-17] and lipoxygenase products (12-hydroperoxyeicosatetraenoic acid and 15-hydroperoxyeicosatetraenoic acid).[18]

The mechanisms underlying enhanced capsaicin responses in chronic cough are not well understood, but responsiveness of unmyelinated airway fibers could be increased through decreasing the activation threshold of the TRPV1 channel, upregulation of TRPV1 expression, or phenotypic switching of myelinated fibers to also express TRPV1.[19] Indeed, one study suggested that TRPV1 expression might be increased in the endobronchial mucosa of patients with chronic cough.[20] However, amplification of responses could also occur in the central nervous system through sensitization of central pathways, failure of inhibitory control mechanisms, or both.[21,22]

Several TRPV1 antagonists have been developed[23]; however, during early-phase clinical trials, some molecules caused hyperthermia[24] and impaired perception of noxious heat.[25,26] SB-705498 is a highly selective and potent competitive antagonist of the human TRPV1 receptor,[27,28] which does not exhibit significant disturbances in temperature perception or control.[29] It has shown activity in a human experimental model of skin hyperalgesia (UVB-evoked inflammation).[29] However, allergen-induced symptoms in patients with allergic rhinitis did not improve with intranasal SB-705498 alone or when combined with fluticasone propionate.[30] Similarly, in subjects with nonallergic rhinitis, it

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Abbreviations used
C2: Concentration of capsaicin inducing at least 2 coughs
C5: Concentration of capsaicin inducing at least 5 coughs
CQLQ: Cough Quality of Life Questionnaire
HRT: Hormone replacement therapy
IQR: Interquartile range
T_{max}: Time to maximum observed plasma concentration
TRPV1: Transient receptor potential vanilloid 1
VAS: Visual analog scale

did not improve symptoms after cold dry air exposure.[31] SB-705498 is rapidly absorbed after oral administration (peak concentrations, 45 minutes to 2 hours) but has a long elimination half-life of 50 to 60 hours. In animals it crosses the blood-brain barrier and therefore potentially has activity in both the peripheral and central nervous systems.

Thus the aim of this study was to assess the antitussive effects of TRPV1 receptor antagonism by using SB-705498 in patients with refractory chronic cough. Capsaicin cough challenges were used to assess airway TRPV1 blockade and combined with 24-hour cough monitoring to assess the translation of this mechanism into reductions in spontaneous cough frequency. Some of these data have been published in abstract form.[32]

METHODS

Detailed methods are provided in the Methods section in this article's Online Repository at www.jacionline.org.

Study design

A randomized, double-blind, placebo-controlled crossover trial was performed comparing a single dose of 600 mg of SB-705498 (6 × 100 mg) with matched placebo. The coprimary end points were cough responses to inhaled capsaicin (2 hours after dose) and objective cough frequency over the 24 hours after dosing. Subjects also rated cough severity and urge to cough on visual analog scales (VASs). Because of the long half-life of SB-705498 (50-60 hours), a 4-week washout separated the 2 treatment periods, and the Cough Quality of Life Questionnaire (CQLQ) was repeated at 14 days after dosing to assess for prolonged treatment effects. The study design is shown in Fig 1.

Subjects

Twenty-one patients with refractory chronic cough (>8 weeks' duration) attending a specialist cough clinic were recruited into the study. All subjects had undergone full investigation and treatment trials for possible causes of cough. Current smokers and exsmokers with a greater than 5 pack-year smoking history were excluded, as were those who did not cough at least 5 times (concentration of capsaicin inducing at least [C5]) after capsaicin inhalation up to a concentration of 250 μmol/L. The study was approved by the research ethics committee (11/H1008/2), and the patients provided written informed consent.

Procedures

Capsaicin challenge. Subjects took single inhalations of doubling concentrations of capsaicin solution (0.49-1000 μmol/L; Stockport Pharmaceuticals Ltd, Stockport, United Kingdom) at 1-minute intervals from flow-regulated nebulizer pots controlled by a dosimeter (Koko dosimeter; DeVilbiss Health Care, Somerset, Pa). Three additional placebo pots (0.9% saline) were randomly placed in the challenge sequence. The concentration of capsaicin inducing at least 2 coughs (C2) and C5 values within 15 seconds of inhalation were recorded. If C2/C5 occurred with placebo inhalation, analyses were performed by treating such data as missing and also imputing the next capsaicin concentration in the sequence.

Ambulatory cough recording. The VitaloJAK cough monitor (Vitalograph, Buckinghamshire, United Kingdom) was used to make 24-hour acoustic recordings from a free-field microphone and contact sensor. Silences and background noise were removed by using validated, custom-written software,[33] and cough sounds were counted with an audio editing package (Audition version 3; Adobe Systems, San Jose, Calif).

Additional end points. Blood samples were collected for pharmacokinetic testing up to 4 hours after dosing and at 24 hours. Subjects rated cough severity and urge to cough on separate 100-mm VASs before dosing and 2 and 24 hours after dosing. The CQLQ, a cough-specific quality-of-life questionnaire, was completed at baseline and 14 days after treatment.[34] Vital signs, electrocardiograms, body temperature, hematology, biochemistry, and adverse events were monitored throughout to assess safety.

Data analysis

Both capsaicin cough responses and 24-hour cough frequency were log-transformed before analysis, and the change from predose measures was calculated. The differences between SB-705498 and placebo were analyzed by using mixed-effects modeling (SAS version 9.2; SAS Institute, Cary, NC), with statistical significance set at the .025 level.

The study was powered for changes in capsaicin sensitivity. Assuming an SD of 0.50 for the difference in logC5 values between active and placebo treatments,[35] the power to detect a 1-sided 2.5% difference in logC5 of 0.35 (>1 doubling dose) is 93% with 24 subjects.

RESULTS

Subjects

Patients' characteristics are summarized in Table I. The majority of subjects were female and middle aged, as is typical of patients presenting with refractory cough. At screening, subjects were highly sensitive to capsaicin; the median capsaicin C5 value was 7.81 μmol/L (range, 0.49-125 μmol/L). Of 21 patients screened and randomized, 2 withdrew after the first treatment period because of symptoms consistent with a viral upper respiratory tract infection. Both patients had received placebo treatment (Fig 2).

Capsaicin cough responses

Treatment with SB-705498 increased C5 values at 2 hours after dosing compared with baseline values (median, +2 doubling doses; interquartile range [IQR], 0 to +2 doubling doses); however, there was no change with placebo treatment (median, 0 doubling doses; range, −1 to +1 doubling doses; Table II and Fig 3 summarize the raw data). The increase in C5 values was similar at 24 hours after dosing (median, +2 doubling doses; IQR, +1 to +2 doubling doses), and again, there was no change with placebo treatment (median, 0.0 doubling doses; IQR, 0 to +1 doubling doses).

The difference between SB-705498 and placebo in the log-transformed change from before dosing was investigated by using a repeated-measures mixed-effects model with fixed-effects terms for treatment, period, subject, and period baselines and interactions between period and time point and treatment and time point. Subject was treated as a random effect in the model, and time point (2 and 24 hours) was treated as a repeated effect. The improvement in C5 values with SB-705498 treatment was significantly greater at 2 hours and borderline significant at 24 hours compared with that after placebo treatment (adjusted mean difference of +1.3 doubling doses at 2 hours [95% CI, +0.3