Evaluation of Comorbid Conditions Among Refractory or Unexplained Chronic Cough Patients in Two Phase 2 Randomized Controlled Trials

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BACKGROUND

- A subset of patients with chronic cough (ie, cough lasting >8 weeks) may have
  - Refractory chronic cough (RCC): refractory to treatment for conditions associated with chronic cough
  - Unexplained chronic cough (UCC): an accurate diagnosis of a condition associated with chronic cough cannot be identified
- Common possible etiologies[1] include
  - Asthma
  - Gastroesophageal reflux disease (GERD)
  - Rhinitis/upper airway cough syndrome
- RCC/UCC patients often endure
  - Years of cough with no symptom relief
  - Multiple investigations involving referrals to specialists
  - Multiple misdiagnoses
  - Unsuccessful treatments with multiple medications

OBJECTIVE

To characterize comorbid diagnoses and prior medication utilization for RCC/UCC subjects enrolled in two randomized controlled studies of the P2X3 receptor antagonist gefapixant

METHODS

- Participants were enrolled in two phase 2 studies
  - Study 1: two-cohort (16 days each), randomized, controlled, dose-escalation, crossover study conducted in the US (NCT02349425)[1]
  - Study 2: 12-week, randomized, controlled, parallel-group study conducted in the US and UK (NCT02612610)[2]
- Randomized patients (≥8 years of age) had RCC or UCC (cough severity visual analogue scale ≥40 mm) as described by American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS) guidelines
- Medical history was recorded at baseline, including previous diagnoses/comorbid conditions and prior therapies (within 30 days of screening and chronic cough treatments within 1 year of screening for both studies)
- The proportion of patients with secondary diagnoses associated with cough (ie, asthma, GERD, and rhinitis) and overlapping of diagnoses was assessed in the pooled patient population

RESULTS

Patients

- In Study 1 (NCT02349425), 29 (Cohort 1) and 30 (Cohort 2) patients were randomized (only unique patients were included in this analysis)
- In Study 2 (NCT02612610), 252 patients were randomized and reported medical history
- Baseline demographics are presented in **Table 1**

Table 1. Baseline Characteristics

	Study 1		Study 2
	Cohort 1 (n=29)	Cohort 2 (n=30)	(n=253)
Age, y (mean [±SD])	63.2 (±7.4)	60.2 (±11.1)	60.2 (±9.9)
Gender ratio			
M:F	4:25	6:24	60:193
Race			
White	28 (96.6%)	28 (93.3%)	234 (92%)
Other	1 (3.4%)	2 (6.6%)	19 (8%)
BMI (mean [±SD])	26.6 kg/m^2 (±4.8)	26.5 kg/m^2 (±4.8)	27.7 kg/m^2 (4.7)
Cough duration, yr (median [range])	15.4 (1-55)	13.2 (2-43)	11.0 (2-56)

Prior Medications

- The most common prior therapies recorded in medical history at baseline included medications for GERD, asthma, rhinitis, and cough (**Table 2**)

Table 2. Prior Medications for Conditions Related to Cough

Study	Medication	Class	N (%)
Study 1 (Cohort 1) (n=29)	Fluticasone proprionate	Corticosteroid	9 (30.0%)
	Omeprazole	Proton pump inhibitor	8 (26.7%)
	Salbutamol	Short-acting beta agonist	7 (23.3%)
	Benzonatate	Antitussive	6 (20.0%)
Study 1 (Cohort 2) (n=30)	Omeprazole	Proton pump inhibitor	10 (34.5%)
	Azelastine hydrochloride	Antihistamine	7 (24.1%)
	Benzonatate	Antitussive	6 (20.7%)
	Montelukast sodium	Leukotriene receptor antagonist	6 (20.7%)
Study 2 (n=252)[a]	Gabapentin	Anticonvulsant/antitussive	28 (11.1%)
	Benzonatate	Antitussive	23 (9.1%)
	Omeprazole	Proton pump inhibitor	21 (8.3%)
	Prednisone	Corticosteroid	18 (7.1%)
	Bromhexine	Mucolytic/congestion	14 (5.6%)
	Azelastine hydrochloride	Antihistamine	14 (5.6%)
	Guaifenesin	Expectorant/congestion	13 (5.2%)

[a]One subject did not report medical history.

Prior Diagnoses and Comorbid Conditions (Studies 1 and 2 Pooled)

Figure 1. Total Prior Diagnoses

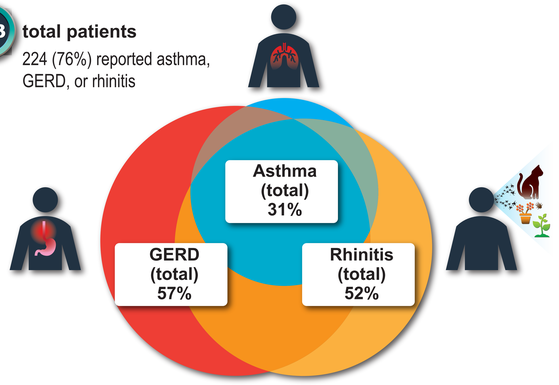
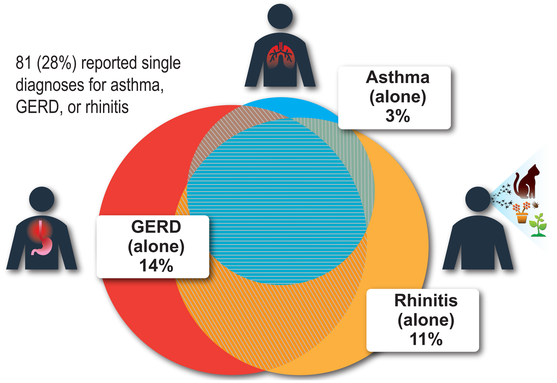
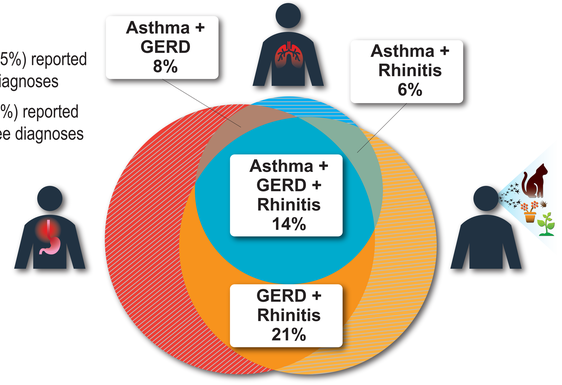


Figure 2. Lone Prior Diagnoses



*293 total patients.

Figure 3. Multiple Prior Diagnoses



*293 total patients.

LIMITATIONS

These studies were not designed to capture full/detailed work up of chronic cough patients (medical history was limited to within 30 days of treatment/1 year for cough treatments)

CONCLUSIONS

Multiple, overlapping co-morbid conditions are diagnosed and treated in patients with chronic cough, even in those who are cared for in specialist centers and in whom the cough remains refractory to such treatments. This represents a very significant burden for patients undergoing multiple investigations and treatment failures

References

1. Irwin RS, et al. *Chest*. 2018;153(1):196-209.
2. Smith JA, et al. *Eur Respir J*. doi: 10.1183/13993003.01615-2019.
3. Smith JA, et al, *Lancet Respir Med*. doi.org/10.1016/S2213-2600(19)30471-0.

Any questions? Please contact Mandel Sher, MD on Twitter @mandel_sher

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