DRUG UPDATE

Gefapixant

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ABSTRACT

Chronic cough lasting for more than 8 weeks can be due to some underlying pathological conditions or can be unexplained. Chronic cough leads to decrease in quality of life. After several investigations and researches it has been found that it can be benefitted by some agents working on cough reflex pathway. One of such agents is, Gefapixant which is an investigational selective P2X3 receptor antagonist. This drug update will describe all the clinical trial data, benefits and potential uses of this novel agent.

Keywords; Chronic cough, Gefapixant, P2X3 antagonist

Article

Chronic cough affects approximately 5–10% of the global population. Chronic cough can be complicated by incontinence, cough syncope, and dysphonia, leading to social embarrassment and subsequent social isolation and depression or anxiety leading to poor quality of life.

Chronic cough can be of two types refractory or unexplained. In some people it can be associated with a treatable underlying cause such as allergic rhinitis, upper-airway cough syndrome, asthma, non-asthmatic eosinophilic bronchitis or gastro-oesophageal reflux disease. Many of these individuals might respond to treatments targeting the primary cause. This is called as refractory chronic cough, while unexplained is the one which is not getting treated and is idiopathic. Currently, no therapies are approved for these conditions, and for treatment of such cases, clinicians often focus on off-label treatments such as morphine, amitriptyline, gabapentin, pregabalin, speech therapy etc. Thus to cover these unmet needs for safe and effective medication, one new development is coming in picture elaborating cough as neuropathic disorder and targetting newly involoved receptors P2X3 in pathophysiology of cough[1].

$P2X_3$ receptors are ATP ion-gated channels located on primary afferent neurons. ATP released from damaged or inflamed tissues in the airways acts on $P2X_3$ receptors of primary afferent neurons, trigger depolarization and action potentials which is then transmitted centrally and results in cough. There are strong preclinical and clinical evidence supporting the role of P2X3 receptors in hypersensitization of the cough reflex. Following diagram explain cough reflex pathways and role of different receptors in mediation of cough reflex[2,3]. (Figure 1& 2)

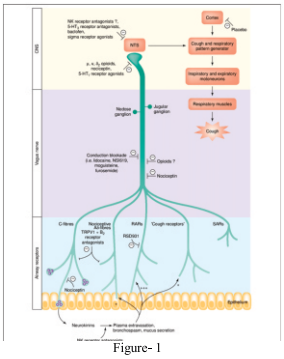

Figure- 1

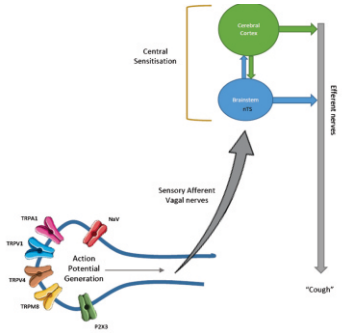

Figure- 2

Preclinical studies had shown that P2X3 receptors, which are present on airway vagal afferent nerves, are countable forhypersensitisationof sensory neurons and mediate the cough reflex, which leads tochronic cough. Preclinical studies were performed to investigate the efficacy of AF-219, to reduce cough frequency in patients with refractory chronic cough and they gave satisfactory results. Gefapixant is a first-in-class, non-narcotic, selective antagonist of the P2X3 receptor. This drug has shown efficacy and was also very well tolerated in phase 2 and phase 3 clinical trials in patients with refractory chronic cough[4,5].

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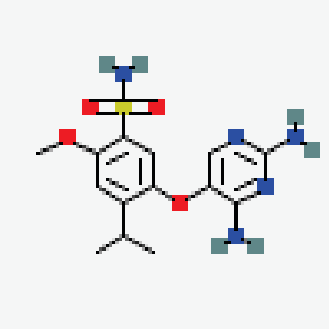
Chemistry of Gefapixant[6]

- Chemical structure of Gefapixant



- Molecular formula- $C_{14}H_{19}N_5O_4S$
- MW: 353.4g/mol
- IUPACname: 5-(2, 4-diaminopyrimidin-5-yl)oxy-2-methoxy-4-propan-2-ylbenzenesulfonamide[6]

In one of the double-blind, placebo-controlled, two-period, crossover study, a computer-generated sequence was used to randomly divide patients with refractory chronic cough in two groups receiving AF-219 (Gifapixant), 600 mg twice a day and placebo (1:1), and then, after a 2 week washout, assigned patients received the other treatment. Patients, health-care providers, and investigators were masked to sequence assignment. Daytime cough frequency (primary endpoint) at baseline and after 2 weeks of treatment using 24 h ambulatory cough recordings was noted. This study showed that Targeting purinergic receptor P2X3 with Gefapixant at a dose of 50 mg twice daily significantly reduced cough frequency in patients with refractory chronic cough or unexplained chronic cough after 12 weeks of treatment compared with placebo. Further development of gefapixant is warranted for the treatment of chronic cough[7].

In another phase 2b, randomised, double-blind, placebo-controlled study in USA and UK again this compound was tested. This was a 12 week study in patients with refractory chronic cough or unexplained chronic cough in age group of 18-80 years who were recruited from 44 primarily outpatient respiratory departments. Recruited patients had refractory or unexplained chronic cough for 1 year or longer, no radiographic chest abnormality, and 40 mm or more on a 100-mm cough severity visual analogue scale at enrolment. According to a computer generated system patients were randomly assigned to receive placebo or oral Gefapixant (in one of three doses of 7.5 mg, 20 mg, or 50 mg twice daily) every day, for 84 days. Changes in cough frequency was assessed after 12 weeks in the full analysis set, along with this adverse events were also monitored to evaluate safety. Dose of 50 mg was found very effective in reducing cough frequency and also was not having a lot of adverse events[8].

	COUGH-1 (Week 12)			COUGH-2 (Week 24)		
	Placebo	Gefapixant 15 mg	Gefapixant 45 mg	Placebo	Gefapixant 15 mg	Gefapixant 45 mg
Efficacy						
N Included in Analysis	222	227	217	419	415	409
Baseline Geometric Mean 24-Hr Cough Frequency (coughs/hr)	22.83	19.86	18.24	19.48	19.35	18.55
Geometric Mean 24-Hr Cough Frequency at Primary Timepoint	10.33	9.66	7.05	8.34	8.10	6.83
Estimated Relative Reduction (%) (95% CI) vs Placebo*	--	1.58 (-16.12, 23.01)	-18.45 (-32.92, -0.86) p=0.041	--	-1.14 (-14.27, 14.02)	-14.64 (-26.07, -1.43) p=0.031
Safety						
N Included in summary (Safety)	243	244	243	433	441	440
% Overall AEs	53%	56%	75%	73%	79%	87%
% Serious AEs	2%	3%	3%	4%	3%	3%
% Taste-Related AE	3%	11%	58%	8%	20%	69%
Estimated relative reduction (%) vs placebo was estimated by 100(exp(diff) - 1), where diff was the difference provided by the analysis of the log transformed variable.						

Two phase 3 trials of Gefapixant which were named as COUGH-1 (NCT03449134) and COUGH-2 (NCT03449147). These were double-blind, randomized placebo-controlled trials for refractory or unexplained chronic cough (RCC/UCC). This table shows the results of these two trials[8].

Treatment with Gefapixant 45 mg BID resulted in significant reduction in 24h cough frequency in participants with RCC/UCC. Serious AEs were infrequent and AEs with Gefapixant 45 mg were most commonly related to taste[9].

In conclusion it can be said that Gefapixant seems to be an efficacious treatment option for chronic cough with an acceptable safety profile and no serious treatment-related adverse events. Still some comparative studies with other available options and extensive research on adverse effect profile is required.

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