Cough in idiopathic pulmonary fibrosis: what is new

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal interstitial fibrosing disease and, despite some well-known risk factors, its cause is still unknown. Cough is experienced by most patients and is commonly chronic and refractory, having a significant impact on quality of life. Its aetiology is complex, combining factors related to interstitial lung disease (ILD) such as an increased sensitivity of cough-sensitive nerves, structural lung changes and inflammation, genetic factors, several comorbidities and medication-adverse effects. Despite the therapeutic advancements in IPF over the past decade with the introduction of antifibrotic drugs that slow disease progression, effective treatment options for cough in IPF remain unavailable. Cough management often relies on empirical approaches based on studies involving chronic cough patients of unspecified causes and ILD physicians' personal experiences. Different classes of medications have been tried over time and, more recently, the focus has turned to neuromodulators and opioids, but several studies have shown suboptimal efficacy in cough. On the other hand, these drugs are associated with significant physical, psychological and economic burdens. However, the future brings us hope to the extent that most current ongoing clinical trials are using new molecules and some have demonstrated promising antitussive effects. This review aims to provide a practical guide to understanding and managing cough in IPF patients, presenting pharmacological and non-pharmacological approaches over time, as well as those treatments that are currently being investigated in clinical settings.

Educational aims

- To review the pathophysiology of cough in IPF.
- To review pharmacological and non-pharmacological approaches to the treatment of cough in IPF.
- To understand the key baseline characteristics associated with response to each therapy for cough in IPF.
- To review new approaches from recent clinical data and real-world studies of therapies for cough in IPF.
- To gain awareness on the practical issues that can impact the choice of therapies in cough in IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and inevitable progressive interstitial fibrosing pneumonia. Causative risk factors are still unknown [1, 2]. Cough is one of the most clinically significant and common symptoms reported by patients with IPF that negatively impacts health-related quality of life (QoL), having not only physical but also psychological and social consequences [3, 4].

Interstitial lung disease (ILD) clinicians are aware of the significant burden of cough, but its frequency or severity is not completely known. Previous studies reported a prevalence of chronic cough (CC) in IPF ranging between 50% and 80%, affirming that the consequences and adverse effects on QoL are similar to the impact of dyspnoea on patients with disabling chronic obstructive pulmonary disease [5]. Other authors have quantified cough events in IPF revealing an average frequency of nine occurrences per hour, with some patients experiencing 39 episodes, predominantly during waking hours, with a significative decrease at night [6].

In a recent prospective study, Saunders *et al*. [3] evaluated cough burden using the Leicester Cough Questionnaire (LCQ) in newly diagnosed IPF patients (n=632) and examined its impact on QoL, uncovering valuable insights. At baseline, the median score was 16.1 (IQR 6.5), greater than described in the general population with CC, and remained stable over the subsequent year in the majority of the patients. Cough showed a weak association with disease severity at baseline (lung function measure by forced vital capacity and diffusing capacity for carbon monoxide) and cough-specific QoL was not associated with subsequent mortality, therefore it conferred no prognostic value [3]. However, regarding cough severity, disease trajectory and IPF prognosis, data are contradictory, and this issue remains a point of contention. In previous studies, cough was an independent factor associated with disease progression [5]. On the other hand, a recent prospective study on IPF and non-IPF fibrotic ILD patients reported that the median baseline cough severity was higher in IPF, evaluated with the visual analogue scale (VAS). Data also revealed an association between a worse cough and gastroesophageal reflux disease (GORD), poor QoL, higher decline in diffusing capacity for carbon monoxide, disease progression and reduced transplant-free survival, as well as an increase in cough severity over time regardless of ILD-specific therapies. Therefore, investigators assumed prognostic implications of cough severity in QoL, disease progression and survival in fibrotic ILD [7].

These results were according to a prospective trial performed by Wu *et al*. [8] in IPF patients. They found a strong negative correlation between cough VAS and LCQ and a positive correlation with the Living with IPF cough domain. Patients with more severe cough (VAS $\geqslant$30 mm) reported significantly poor QoL evaluated by LCQ and Living with IPF cough. Specifically, regarding a possible implication on prognosis, an association was found between a worse baseline cough VAS score and poor survival in both univariate and multivariate analyses. In contradiction with the previous study, authors found that the sub-group of patients with a baseline cough VAS score $\geqslant$30 mm experienced a significative improvement in VAS score with antifibrotic treatment (nintedanib, −9.7 mm; pirfenidone, −12.4 mm), but this was not reflected in QoL measurements [8].

However, we want to highlight that some of the discrepancies found between studies could be related to methodological issues such as different methods and tools used to assess and measure cough severity as well as the data collected that included objective (cough count) and subjective parameters such as patient-reported outcome measures.

Pathophysiology of chronic cough in IPF

The mechanisms underlying cough in IPF are not yet completely known and understood (figure 1). The moment of IPF diagnosis, as well as cough behaviour during the disease, have not been systematically studied and described. Although the pathophysiology of CC in IPF remains unclear, it likely involves a complex interplay of mechanisms. These include factors related to the ILD itself but also the influence of respiratory and non-respiratory comorbidities and medication adverse effects [3, 4]. Different disease-specific mechanisms have been proposed, including mechanical and neurosensory changes. These encompass structural lung alterations and architectural distortion of the airways and lung parenchyma,

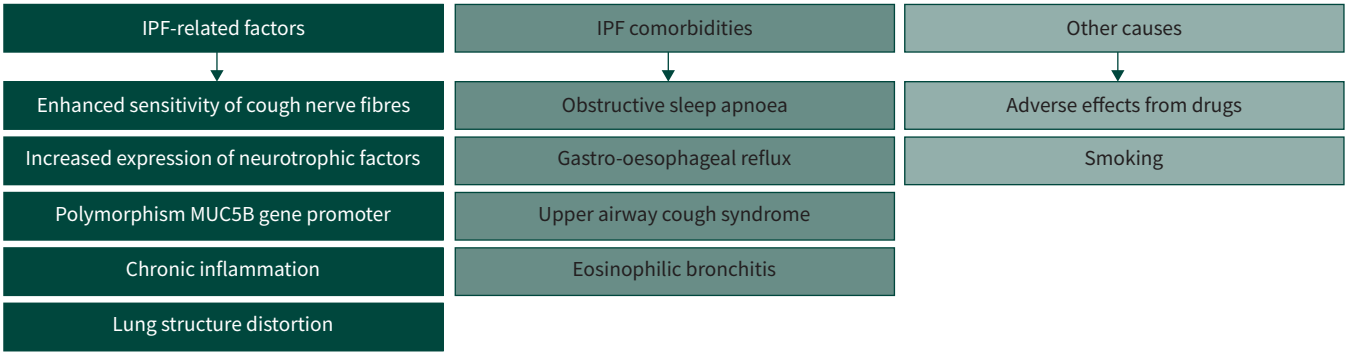

Figure 1 Pathophysiological mechanisms involved in cough in idiopathic pulmonary fibrosis (IPF). Cough is multifactorial. Disease-specific mechanisms were proposed, such as mechanical and neurosensory changes including structural lung architectural distortion, an exaggerated neurogenic cough reflex leading to heightened sensitivity of cough-sensitive nerve fibres, and increased expression of neurotrophic factors, chronic inflammation, and genetic polymorphisms. Several comorbidities also contribute to cough as well as smoking and the adverse effects of some drugs [3, 4, 9, 10].

mucus hypersecretion, an exaggerated neurogenic cough reflex leading to heightened sensitivity of cough-sensitive nerve fibres, and increased expression of neurotrophic factors like nerve growth factor and brain-derived neurotrophic factor [9]. Other causes are chronic inflammation and genetic polymorphisms, namely the minor allele of mucin-5 subtype B promoter (MUC5B) that was associated with an elevated cough burden in some studies [4, 10], but this has not been replicated in larger cohorts [3]. CC in IPF is multifactorial and despite all these specific drivers related to the ILD, patients can present several comorbidities that may contribute to the presence, worsening and receding of cough, including obstructive sleep apnoea (OSA), GORD and airway diseases. A detailed history of inhaled exposures and the use of drugs should also be considered in this broad approach. Therefore, all these causes must be sought and treated appropriately to achieve cough control in IPF [9].

Cough treatment over time

Despite the therapeutic progress achieved in IPF using antifibrotic drugs which slow disease progression, there is still no widely accepted or effective treatment for cough. In fact, neither non-pharmacological measures such as pulmonary rehabilitation nor antifibrotic drugs positively affect QoL and symptom control in IPF patients [3].

When managing CC in IPF, in addition to treating the underlying disease, adjunct interventions should be considered to address secondary causes of cough related to comorbid conditions. However, given the limited understanding of the underlying mechanisms, several molecules were used over time, often relying on empirical approaches based on studies involving CC patients of unspecified causes and ILD physicians' personal experiences. Different drug classes such as oral antacids, inhaled corticosteroids, neuromodulators and opioid central inhibitors were used, but have shown no evidence of clinical benefit and suboptimal efficacy in controlling cough [10]. On the other hand, they were associated with significant physical, psychological and economic adverse effects on IPF patients [4].

Considering the absence of international guidelines to allow the best clinical decisions or randomised head-to-head trials comparing different treatment options for cough in IPF, we aim to summarise the latest data currently available to help clinicians in decision-making. This review will focus on non-pharmacological and pharmacological options over time, as well as the emerging pharmacological approaches that are being developed and investigated in ongoing clinical trials and have demonstrated promising antitussive effects.

Treating cough in IPF

The underlying disease

Antifibrotics

IPF treatment aims to slow disease progression, increase survival and limit the burden of symptoms, including activity-related dyspnoea, fatigue and CC [9]. Since cough is one of the major symptoms, a relevant and obvious question was whether treating the underlying disease would help reduce or eliminate cough.

Over time several therapies have been investigated and used with variable success rates regarding disease progression and symptom control. Still, IPF treatment paradigm has undergone a revolution in the last decade with the availability of two antifibrotic drugs, nintedanib and pirfenidone, which are still the approved therapies for IPF as they have demonstrated efficacy in slowing lung function decline [11, 12]. Although symptom control was not a primary endpoint and their impact on cough was not evaluated as a primary outcome in major antifibrotic clinical trials, in a post hoc analysis of patient-reported outcomes data from the INPULSIS trial, nintedanib did not seem to improve cough related to QoL [13].

On the other hand, the ASCEND trial demonstrated that cough was more common in the placebo group, raising the possibility that pirfenidone may have an effect on cough [12]. This was confirmed by Azuma *et al*. [14] in an exploratory analysis of a phase 3 trial in IPF patients treated with pirfenidone for 52 weeks. They found that the drug significantly suppressed cough and dyspnoea in a subpopulation of patients with forced vital capacity greater than 70% and peripheral oxygen saturation less than 90% at baseline [14]. Later, in a prospective, observational study in 43 treatment-naïve IPF patients with CC, pirfenidone showed a significant reduction in both objective 24-hour cough counts, subjective cough severity and improved cough-related QoL. These changes were clinically meaningful to patients. Moreover, this study was the first to show a significant improvement in cough by a pharmacologic treatment using both objective and subjective measures in IPF patients [15]. In addition, in a recent prospective study on cough in IPF patients, the authors found that the sub-group with a baseline cough VAS score $\geqslant$30 mm

experienced a significative improvement in VAS score with antifibrotic treatment (nintedanib, −9.7 mm ($p<0.001$); pirfenidone, −12.4 mm ($p<0.001$)), but this was not reflected in QoL measurements [8].

Management of comorbidities

As stated previously, there are many things that could cause CC within IPF, so clinicians must search for and control comorbid conditions that may contribute to CC. A recent statement on CC also presents several treatable traits to consider such as obesity, smoking, angiotensin-converting enzyme inhibitors, eosinophilic airway disease, GORD, upper airway symptoms and OSA [16]. However, International guidelines on the management of IPF provide few recommendations addressing cough treatment and the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociación Latinoamericana de Tórax Clinical Practice Guideline consensus recommends that patients may benefit from palliative care to help with symptom management [2].

As a possible cause, angiotensin-converting enzyme inhibitors should always be excluded, but symptoms may take 4 weeks to improve after drug removal [16]. GORD is highly prevalent in IPF and responsible for microaspirations (acid and non-acid) that probably induce epithelial damage and may cause fibrosis, but gastric symptoms are often absent [17]. Current evidence supports that treatment should be based on lifestyle modifications and antiacid therapy (proton pump inhibitors for 4 weeks) only in the presence of peptic symptoms. If refractory, patients should be referred to gastroenterology [16]. OSA is common in IPF and intermittent hypoxaemia may promote profibrotic mechanisms [18]. Previous studies have revealed that CC is more prevalent in OSA, but can be improved by continuous positive airway pressure therapy. On the other hand, upper airway obstruction could increase the trans-diaphragmatic pressure promoting GORD. Therefore, GORD, CC and IPF can probably be improved by OSA treatment [19]. As a conclusion, we must not forget all the possible and common causes of cough in these patients, even though they have fibrosis.

Non-pharmacological treatment

Multimodality speech therapy

An established treatment for unexplained CC, as it has been demonstrated to decrease cough frequency and improve QoL [20]. Additionally, physiotherapy, speech, and language therapy have shown similar benefits in suppressing cough and improving sleep. However, to achieve better results they must be used alongside neuromodulator medications such as gabapentin or pregabalin to decrease cough reflex sensitivity [21]. Regarding specifically IPF patients, evidence is scarce but those may represent a suitable treatment.

Pharmacological treatment

Oxygen

Some authors have reported that based on their practical experience many patients with IPF and hypoxaemia can have a dramatic improvement in cough – even sometimes resolving it – with oxygen [9].

After treatments aimed at ILD and respiratory comorbidities, scientific societies have made recommendations regarding the consideration of neuromodulator therapies as an option for refractory cough.

Pregabalin

A combination of pregabalin and speech therapy improved cough and QoL more effectively than speech therapy alone [15]. A randomised controlled trial demonstrated that a combined intervention exceeded the benefits achieved with speech therapy alone in refractory CC treatment, and observed benefits were related to temporary improvements in cough-specific QoL and cough frequency leading to a more significant improvement in cough severity [22].

Gabapentin

In a double-blind, randomised, controlled trial, gabapentin has shown efficacy in reducing cough severity and a significative improvement in cough-specific QoL in patients with refractory chronic cough (RCC) compared to placebo. Despite the low starting dose (100–300 mg) which then escalated to a three-times-daily schedule, 31% of patients experienced adverse events such as confusion, dizziness, dry mouth and fatigue [23].

Amitriptyline

In a prospective study, Jeyakumar *et al.* [24] evaluated the effectiveness of amitriptyline (10 mg day) *versus* cough suppressants (codeine/guaifenesin every 6 h) in CC for 10 days. In the amitriptyline group, the majority of patients achieved a complete response in the subjective rate of reduction in the frequency and cough severity. None of the codeine/guaifenesin patient group achieved this result [24]. Later, in a

retrospective review on the outcomes of idiopathic cough treatment with amitriptyline over a short and a long term (3-years), 67% of patients reported ⩾50% improvement at 2.6 months and at a follow-up 2 to 3 years later, 53% reported a ⩾50% improvement. However, only 34% of the patients were still taking amitriptyline, due to the side effects [25].

Opioids

Opioids are commonly used in symptom control in IPF patients in terminal stages, including chronic and refractory cough. Despite being considered effective antitussive modulation agents there is a lack of robust evidence based on well-designed controlled clinical trials regarding their efficacy and the adverse effects related to long-term opioid-class drugs use in early disease subjects, as well as other problems such as physical dependence [26].

Morphine

For a long time, there was scarce evidence based on published randomised controlled trials evaluating the efficacy and safety of opiates in refractory CC, and commonly patients with significant lung diseases were excluded. For this reason, recommendations regarding the use of morphine for CC are not uniform. Furthermore, in IPF, its use was frequently based on a case-by-case basis in patients who have failed to respond to other therapies and whose cough has severely impaired quality of life.

In a previous study on slow-release morphine sulphate (5 mg twice daily for 4 weeks) in 27 patients with CC, it was noted a significant improvement in LCQ and a rapid and high reduction (by 40%) in daily cough scores among patients on opioid. It was performed an open-label extension of the core study with a dose escalation to 10 mg twice daily (12 patients), and after 3 months, there was a similar improvement in cough between the 5 mg and 10 mg groups. Hence, morphine sulphate was considered an effective antitussive in intractable CC at both doses [27].

The results of the PACIFY COUGH study have recently been published, a phase 2, multicentre, double-blind trial in IPF patients with CC [28]. 44 patients were randomly assigned to placebo (twice daily) or controlled release morphine 5 mg orally (twice daily) for 14 days, followed by a crossover after a 7-day washout. In the intention-to-treat population, morphine reduced objective awake cough frequency by 39.4% (95% CI −54.4 to −19.4; p=0·0005), and the mean daytime cough frequency from baseline, whereas cough rates did not change with placebo. So, these findings revealed that morphine might be an effective treatment for cough in patients with IPF. However, adverse events were significantly higher in the morphine group compared to placebo and were mainly nausea (14%) and constipation (21%) [28].

Nalbuphine extended-release (NAL-ER)

An extended-release opioid analgesic with antagonist activity at the μ-opioid receptor and agonist activity at the κ-opioid receptor. It has been thought that this oral form could present a potential therapeutic benefit on opioid-based drugs while minimising adverse events, and previous studies have demonstrated its efficacy on CC in IPF by 77.3% [29].

Those findings were corroborated by Maher *et al*. [26] in a randomised, double-blind trial comparing the antitussive effect of nalbuphine *versus* placebo in 41 IPF patients with CC in two 22-day treatment periods with a 2-week washout. NAL-ER was started at 27 mg once daily and titrated up to 162 mg twice daily. Results showed a rapid and significant reduction in objective daytime cough frequency during the NAL-ER treatment (75.1%) *versus* the placebo period (22.6%). Similar results were reported for 24-hour objective cough frequency and improvements were seen in patient-reported outcome measures (cough severity and frequency and breathlessness). However, adverse effects (nausea, fatigue, constipation and dizziness) were more common with NAL-ER and led to drug discontinuation in 23.6% of the patients [26].

More recently, a phase 2 study on the efficacy and safety of NAL-ER for the treatment of cough is underway to test whether the drug is safe and effective in IPF patients. NAL-ER will be compared with a placebo in 44 randomised subjects submitted to two treatment periods (for 3 weeks) followed by a 2-week washout. Assessments will include blood and urine sampling for safety tests and blood sampling for determining the drug's blood levels. A questionnaire will be used to determine symptom severity (cough, breathlessness, fatigue) and subjects will wear a portable cough monitor to measure the frequency of cough episodes, including at night [30].

Prednisone

In previous studies, corticosteroids have not shown a positive impact on survival or lung function in IPF patients [31]. A significant cough reduction was observed with short courses and low doses of prednisone

(10 to 20 mg for 2 weeks), and these results were corroborated using moderate doses for 4 weeks, with a decrease in cough severity and sensitivity to capsaicin observed in six patients with severe IPF cough [9]. However, besides this potential benefit, currently, no high-quality data supports the recommendation for steroid use in IPF cough.

Inhaled sodium cromoglycate

A mast cell stabiliser, historically used in asthma treatment. It has been demonstrated to decrease sensory c-fibre and inflammatory cell activation which could affect CC [32]. Birring *et al*. [33] conducted a phase 2 proof-of-concept trial to determine the effects of aerosolised cromolyn sodium in patients with IPF and cough. Results were very encouraging, revealing that at 14 days, the frequency of mean daytime cough was reduced by 31.1% compared to placebo, with good tolerance. Hence, inhaled aerosolised cromolyn sodium could be a treatment option for CC in IPF [33]. However, a subsequent and larger study failed to confirm these findings. Martinez *et al*. [34] performed a phase 2b study to determine the efficacy, safety, and optimal dose of inhaled RVT-1601 in the treatment of CC in IPF. 108 patients were randomised to receive 10 mg, 40 mg and 80 mg of RVT-1601 three times daily or placebo for 12 weeks and 61.1% completed double-blind treatment. No significant differences were observed in changes from baseline cough count, severity and QoL score between RVT-1601 and the placebo groups, but the drug was well tolerated. So, inhaled cromolyn sodium did not yield a significant improvement in CC in patients with IPF [34].

Thalidomide

Thalidomide acts as an anti-inflammatory, anti-angiogenic and tumour necrosis factor-α inhibitor, and these properties make it a treatment option for certain malignancies and auto-immune diseases [19]. Based on this knowledge, authors have hypothesised that it could have an anti-inflammatory or immunomodulatory effect on IPF or airway sensory afferent nerves and could be considered as a treatment for cough in IPF patients, despite the known side effects (dizziness and neuropathy) [15, 31]. Horton *et al*. [35] performed a 24-week trial to determine the efficacy of low-dose thalidomide in cough in 23 IPF patients. Results showed benefits with improvements in cough severity and respiratory QoL (evaluated by cough quality of life questionnaire and VAS) in patients treated with thalidomide *versus* placebo. However, adverse events were reported in 74% of patients on the drug (22% under placebo) mainly constipation, dizziness and malaise [35]. So, despite these benefits, evidence supporting thalidomide as a treatment for CC is limited, and currently it is not recommended as a routine treatment of cough in IPF.

Interferon-α (IFN-α)

Lutherer *et al*. [36] performed a proof-of-concept trial using low-dose oral IFN-α in 12 IPF patients for 12 months (6 with CC) to test the hypothesis that it might slow disease progression by inhibiting fibroblast replication and collagen production. They found that five of the six subjects reported an overall improvement within 2–3 weeks after initiating the treatment and five of those who completed the LCQ had a significative improvement in the total score. These results suggested that the drug might be effective in treating cough in IPF, however, no more studies have subsequently been conducted with IFN-α in IPF and more representative and long-term studies are required to assume robust conclusions [36].

Azithromycin (AZT)

Different studies have demonstrated contradictory results regarding the efficacy of AZT in CC. Guler *et al*. [37] performed a double-blind trial to determine AZT safety and efficacy in cough in IPF. 25 patients were randomised for two 12-week periods (azithromycin 500 mg three times per week or placebo three times per week) and 20 patients completed the study. There were no significant changes in LCQ or VAS scores between groups and no differences were found between the AZT and placebo periods for changes in polygraphy-measured cough frequency. On the other hand, gastrointestinal adverse effects were more frequent with AZT (diarrhoea, 43% *versus* 5%; p=0.03), so this trial did not support the use of low-dose AZT for CC in IPF patients [37].

Inhaled carcainum chloride

A quaternary derivative of the local anaesthetic lidocaine. A randomised, double-blind, placebo-controlled trial studied the effect of aerosolised carcainium chloride (VRP700) in CC in eight patients with idiopathic interstitial pneumonia. It was found that the drug improved cough and QoL in hospitalised ILD patients, without significant side effects [38]. However, larger studies are needed to reach more reproducible conclusions.

Recent targets and molecules

There is an increasing understanding of the neuropathic basis of cough and fibrotic processes in IPF. However, based on the most recent knowledge, chronic hypersensitivity cough in IPF depends on

heterogeneous mechanisms and must be considered distinct from other chronic hypersensitivity coughs. This provides the need for new potential therapeutic targets. Therefore, we will briefly describe the current ongoing investigations and potential treatments for CC in IPF.

P2X3 inhibitors

P2X3 receptors are ATP ion-gated channels expressed by airway vagal afferent nerves involved in sensory neurons hypersensitisation and cough reflex leading to CC [39, 40].

Gefapixant (P2X3 receptor antagonist)

Previous trials in RCC patients demonstrated a significant reduction in cough frequency. The most common adverse events were taste disturbance (dysgeusia and ageusia) [39, 40]. However, in IPF patients, gefapixant was not associated with a significant improvement in CC [41].

Sivopixant (P2X3 receptor antagonist)

In a 2b, randomised, double-blind, placebo-controlled trial on the effect of sivopixant in RCC the results did not demonstrate a significant difference between this drug and placebo concerning changes in cough frequency. Adverse events increased with higher doses and were mild-to-moderate taste disturbances [42].

BLU-5937 (selective, non-competitive P2X3 receptor antagonist)

First, in a Guinea pig cough model, BLU-5937 significantly reduced cough in a dose-dependent fashion. Later, in a phase 1 trial, some patients reported taste alterations [43]. Then, in a phase 2b trial in RCC patients, changes in 24-h cough frequency were observed, and the benefit was directly proportional to dose increase. Mild adverse effects were reported but not related to the dose [44].

Transient receptor potential vanilloid 1 antagonist (TRPV1)

A previous trial to assess the antitussive effect of a TRPV1 antagonist (SB-705498) in patients with RCC has failed [45]. However, in a subsequent study, the molecule (XEN-D0501) substantially reduced maximal cough responses to capsaicin *versus* placebo, but not on spontaneous awake cough frequency [46].

NTX 1175 (permanently charged sodium channel blocker)

Presents a broader mechanism than P2X3 antagonists and has shown significant antitussive effects in preclinical models of cough. There is an ongoing phase 2a trial to assess the efficacy, safety, tolerability, and pharmacokinetic profiles of inhaled doses of NOC-100 in patients with chronic or acute cough, regardless of the cause [19].

AX-8 (transient receptor potential melastatin 8 agonist (TRPM8))

Results of a randomised, double-blind, placebo-controlled, crossover study in RCC patients revealed that on day 1, AX-8 reduced cough frequency within 15 min, and more than the placebo over 2 h and 4 h [47].

Neurokin-1 receptor antagonists

Aprepitant

In a trial performed on lung cancer and cough patients, cough frequency improved with a 22.2% reduction over placebo while awake, by 30.3% over the 24 h and 59.8% during sleep, and patient-reported outcomes all significantly improved [48].

Orvepitant

In a phase 2 pilot study (VOLCANO-1) in RCC patients a statistically and clinically significant improvement in objective daytime cough frequency and severity and QoL were observed [49]. Results were confirmed in a phase 2b study on 275 RCC patients, achieving significant improvements in patient-reported outcomes: LCQ, VAS and urge-to-cough VAS. Orvepitant was safe and well-tolerated [50].

BW-031 (cationic sodium channel inhibitor)

The molecule was effective in reducing cough counts by 78–90% when applied intratracheally or by aerosol inhalation in Guinea pigs with airway inflammation (produced by ovalbumin sensitisation), suggesting a new clinical approach to treat cough [51].

Despite the previous guidelines on CC management, the subject remained a concerning and challenging area with limited evidence. However, a recent British Thoracic Society statement on CC highlights that CC treatment should be based on patients' phenotype and disease-treatable traits, on a personalised treatment basis. Nevertheless, they also reinforce the need to treat and control other comorbidities and the possibility of using non-pharmacological therapies in a complementary way [16].

Besides all the specific pathogenic mechanisms driving cough in IPF, investigators have focused on the significant contribution of heightened cough sensitivity, as seen in other causes of RCC, and this is proven by the enormous scientific research in this field. New neuromodulating therapies are constantly being developed and some have shown promising results. As an example, gefapixant is currently being used in Japan and has been approved for RCC in the USA, but as seen previously its efficacy was not demonstrated in IPF patients.

In addition to these recent studies on new drugs and molecules, in the future other targets involved in cough signalling pathways in IPF such as nerve growth factor, calcitonin gene-related peptide or interleukin-6 will probably be considered and tested. Another relevant question is these drugs' and molecules' effects on underlying fibrotic processes, besides cough control.

Current and high-quality evidence presents opioids (low-dose morphine) and neuromodulators (gabapentin/pregabalin) as major options for the treatment of RCC [16]. However, concerning specifically IPF-related cough, there are no proven treatments; but as seen before, Wu *et al*. [28] have recently shown that low-dose controlled-release morphine was effective in reducing objective awake cough frequency and improving patients' QoL. Therefore, despite the contribution of this study in extending the knowledge on this field, there is still an absence of recommendations to guide cough treatment in IPF patients, and longer-term studies should be conducted to confirm these findings, to establish the durability of treatment and long-term impact on cough and adverse reactions.

Conclusion

Chronic cough in IPF is a major problem for patients and ILD physicians. To date, many drugs primarily used in the treatment of refractory CC have been tried in IPF-related cough. However, most of the trials were small and time-limited and have not demonstrated great efficacy, with considerable adverse effects and poor safety profiles. In addition, it is noteworthy that currently evidence is still limited and there is no consensus regarding the treatment of IPF-related cough in published guidelines for the management of ILD that can aid clinicians in deciding the best treatment for this serious symptom.

These facts emphasise the urgent need for further research in this field and the study of new approaches for treating cough in IPF. In the future, larger scale and longer duration trials should be addressed to explore and understand the pathophysiological mechanisms of cough in IPF, confirm former encouraging and promising results, develop new effective antitussive treatments and test their long-term efficacy, security and side effects. In addition, in new clinical trials on IPF drugs, cough and QoL should also be included as primary outcomes and measured using validated and reliable instruments. An effort must be made to achieve improvements in the treatment of this condition, and a renewed focus should be to achieve better symptom control allowing an improvement in IPF patient's quality of life, as cough interventions are unlikely to affect survival.

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