Conclusion
Lessons from the novel D_2_ dopamine receptor, β_2_-adrenoceptor agonist, Viozan™: chronic obstructive pulmonary disease and drug development implications

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Abstract
The development of novel drugs for the treatment of chronic obstructive pulmonary disease (COPD) poses significant challenges. The mechanisms through which the chronic symptoms of COPD arise are poorly understood, making identification of potential therapeutic targets and in vivo evaluation of potential therapies extremely difficult. Despite these challenges, a unique approach of combined D_2_ dopamine, β_2_-adrenoceptor agonism was identified as a valid potential target for the treatment of key COPD symptoms, the therapeutic potential of which was investigated in a series of preclinical evaluations. Subsequent clinical assessment has amassed a wealth of data from over 4000 patients, providing valuable insights into COPD, clinical trial design and the value of patient self-assessment tools.

TACKLING A CHRONIC PROBLEM

While no drug can halt the progression of chronic obstructive pulmonary disease (COPD), patients currently rely on a combination of bronchodilators and anti-inflammatory agents to manage their disease (1,2). Drugs approved for this indication were, however, originally developed for the treatment of asthma, despite the differing aetiology and pathophysiology of the two conditions. Due to decades of research in asthmatic patients, bronchodilators are now available that can afford patients with COPD some degree of relief. In a disease characterized by limited airway reversibility, however, this approach can only be met with limited success. With increasing recognition of the need to address a range of key symptoms (3), it is evident that specific therapy tailored to treat a spectrum of COPD symptoms is urgently required. Recognition of this outstanding need has led to considerable research efforts in recent years and a number of potential new therapies have been investigated.

IDENTIFICATION AND ASSESSMENT OF NOVEL AGENTS

The mechanisms through which the chronic symptoms of COPD arise remain poorly understood, making identification of therapeutic targets extremely difficult. Despite this challenge, efforts to identify novel solutions have been intense. Dopamine is a peripheral neurotransmitter that can modulate the activity of sensory nerves. This raises the possibility of inhibiting the sensory nerves in the lung, thought to be responsible for reflex-induced COPD symptoms (4). Dopamine agonism was therefore identified as a potential target for the treatment of key COPD symptoms.

Sibenadet HCl (Viozan™, AR-C68397AA) is the first of a new class of dual D_2_ dopamine receptor, β_2_-adrenoceptor agonists. This novel agent represents the first drug engineered specifically to combine the benefits of conventional β_2_-adrenoceptor agonism with the sensory modulatory effects of a dopamine agonist in a single agent. It is now known that the potential of this therapeutic approach did not translate into sustainable
Clinical efficacy (5). Although initial benefit appeared positive, a reduction in efficacy over time was apparent. Tachyphylaxis to β2-agonists has not been previously documented in COPD, but in these studies this phenomenon may have occurred due to potency of the compound, as a result of the unique properties of sibenadet or other unidentified issues. The relatively late onset of tachyphylaxis may be due in part to the particular endpoints studied in the trials and their sensitivity to highlighting a developing tolerance to the compound. Despite these disappointing results, however, a great deal of important information and key findings have arisen from the sibenadet development programme.

Investigation of the hypothesis that stimulation of D2-receptors on sensory nerve endings in the airways would inhibit afferent activity and consequently suppress key COPD symptoms (breathlessness, cough and sputum) was hampered by a lack of satisfactory animal models of COPD. New experimental paradigms were therefore required in order to test this idea. The D2 agonist properties of sibenadet were extensively evaluated in a comprehensive programme of in vitro and in vivo investigations, which confirmed the ability of sibenadet to inhibit reflex tachypnoea, cough and mucus (4). Most recently, the presence of D2 dopamine receptors on the sensory neurons of thoracic dorsal root ganglia has been demonstrated, strengthening the theoretical value of dopamine agonism in respiratory disease (6).

Despite this substantial body of technically demanding work, in vivo studies may not predict the human experience. Therefore, these data could only be interpreted as providing an indication of the potential clinical effect of sibenadet. Studies of the clinical pharmacology of sibenadet were thwarted by the lack of an inhaled dopaminergic antagonist suitable for use in humans and these data were therefore not available to guide clinical investigation of sibenadet in the patient population.

Challenges in the Clinical Evaluation of Sibenadet and Lessons Learned

Assessing new treatments in COPD can be as fraught with difficulty as the preceding pharmacological studies. Crucial to any clinical trial is the selection of the correct endpoint. Clinical evaluation of sibenadet assessed three major parameters, key COPD symptoms, lung function and adverse events. Some novel approaches were developed in order to address specific needs within the development programme.

Spirometry is commonly used for testing and quantifying pulmonary function, with FEV1 the most often utilized measurement to assess the effect of an intervention on airway obstruction. Reliance on FEV1 measurements stems from routine use in patients with asthma, where this measure is used to demonstrate improvement in clinical trials. However, although this measurement is widely used in clinical trials of COPD therapy, it may be less useful for predicting patient improvement, as patients with COPD by definition have limited reversibility of airway function. In addition, there is no evidence to suggest that the change in FEV1 with treatment necessarily parallels changes in perception of COPD symptoms. Adequate evaluation of the benefits of a dual D2/β2-agonist required a shift in focus from reliance on FEV1 as the sole measure of efficacy to incorporating a novel approach to assessing symptomatic benefit. As no widely accepted assessment approach existed, a new instrument that was simple and easy to use was required. The Breathlessness, Cough and Sputum Scale (BCSS) was therefore developed.

Assessment of Key Symptoms – The Breathlessness, Cough and Sputum Scale

This patient-reported outcome approach was designed to meet a specific need, i.e. to assess change in patient symptoms on a daily basis in response to therapy. It was used in Phase II clinical evaluations and the reliability, reproducibility and validity of this approach was subsequently established (6). The BCSS was therefore able to identify early clinical potential and subsequently provided clear conclusions regarding long-term efficacy in Phase III evaluations. The co-primary endpoint selected for large-scale clinical investigation was change in BCSS total score from baseline to the final 4 weeks of treatment. This distinction was considered important in order to detect a continuing effect in patients with a chronic disease such as COPD. The necessity for this approach was highlighted by the study results, as the large changes in patient symptoms seen at the start of the study would have influenced the study outcome had the whole treatment period been used as the primary endpoint (5). It was, however, considered important to collect data throughout the study period in order to describe ongoing changes and to enable demonstration of patient progression or deterioration.

Statistical analyses have demonstrated a correlation between patient and physician opinion of efficacy, change in HRQL (as determined by the SGRQ) and BCSS scores (7). These analyses have therefore enabled interpretation of a clinically meaningful change in BCSS total score and established the BCSS as a potentially valuable tool for assessing symptomatic benefit of treatment. This scale may also provide a valuable aid to diagnosis when used in combination with spirometric assessments; as indicated in the GOLD guidelines, chronic cough and mucus are often overlooked as diagnostic symptoms (3). Use of the BCSS in patients at high risk of developing COPD (such
as long-term smokers) in order to determine the degree of symptomatology present might act as an indicator that further patient evaluation is required. The BCSS also has potential application as an aid to treatment decision-making as it acts as an ongoing summary of the patient's condition. Further assessment and validation for these applications would, however, be required.

A possible additional value of the BCSS became evident through sub-analysis of study data as the total score appeared to be predictive of an exacerbation event in the subset of patients who had experienced an exacerbation (7). Mean BCSS scores begin to increase some days prior to an exacerbation and are able to track progress to resolution. Further investigations need to be conducted to investigate what is, as yet, only a hypothesis. In particular, determination of both the sensitivity and specificity of using changes in BCSS total scores to predict an exacerbation is required. Exacerbations and their treatment are still poorly understood, but the ability to track symptom changes, with a view to earlier recognition and intervention, may decrease overall costs by reducing the need for hospitalizations or emergency room (ER) visits. A greater understanding of exacerbations in general would be of considerable value and investigation of the role of gender differences, disease subtype, disease severity, exacerbation severity and individual symptoms driving an exacerbation is warranted in future clinical studies.

STUDY DESIGN

Being the first of a novel class of agents, determining optimal trial design for early clinical evaluation of sibenadet posed particular problems. While the Phase II programme achieved the objectives of demonstrating proof of concept and dose-relationship with sibenadet treatment, the promising results demonstrated in these early clinical evaluations were not sustained over the course of the longer-term studies (5,8). It is now clear that Phase II studies of longer duration would have provided greater information on the clinical potential of sibenadet. The disappointing results obtained from Phase III evaluation of sibenadet could not have been fully anticipated from the 6-week Phase II study, highlighting the fact that a study duration typical for assessment of asthmatic patients is not necessarily appropriate for the COPD scenario. This is, of course, dependent on the objective of the study. For instance, assessment of changes in HRQL may require a longer investigation period than assessment of short-term changes in lung function. Although no surrogate markers of treatment effect have yet been defined in patients with COPD, successful identification of such markers would represent a significant advance, thereby allowing effective identification of early clinical potential and avoiding unnecessary burden on patients.

Interpretation of the sibenadet Phase III data was complicated by the marked improvements in BCSS and SGRQ scores amongst patients receiving placebo (5). This effect may be explained by the well-known positive response of many patients, irrespective of therapy, to the increased levels of care experienced during participation in a clinical trial (9). In addition, when recruiting patients with symptoms or frequent exacerbations, it is possible that a proportion of the study population will be recovering from an exacerbation during the study and over time will demonstrate improvement. Patients may take many weeks, or even months, to recover fully from an exacerbation and therefore, despite carefully defined exclusion criteria, this potential problem is a feature of the COPD population that will need to be considered in all future studies. Although the recruitment requirements and randomization procedures should ensure that the effects of ongoing exacerbations are equal in both treatment groups, additional steps could be taken to limit this possibility. Exclusion criteria could be tightened (e.g. by excluding patients who have had an exacerbation within the previous 3 months), but this may impact on patient recruitment and would not necessarily ensure patients were in a stable condition. A longer baseline period could be considered, but the benefits must be weighed against the practical disadvantages. This approach may also raise ethical issues by requiring patients to be off some of their usual medications for a longer period than usual, which could actually induce an exacerbation.

LUNG FUNCTION

With increasing recognition of the need to manage key COPD symptoms and to identify therapeutic approaches other than simple bronchodilation, it is apparent that reliance on FEV1 as the most relevant measure for determining therapeutic benefit in COPD requires reassessment. In the case of sibenadet, the BCSS provided important additional information regarding long-term clinical efficacy. As assessment of forced expiratory volume in one second (FEV1) is a widely recognized and accepted study endpoint, it may not be possible (or advisable) to move away from this approach entirely, but rather to recognize its limitations and consider additional efficacy assessments. The complexity of this chronic disease may, however, necessitate the use of multiple endpoints in order to determine the value of future therapeutic strategies adequately.

CONCLUSIONS

What then have we learned during the development programme for sibenadet? It is apparent that novel pharmacological models offer insight into disease mechanisms but their translation to the bedside is
complex and can be disappointing. Confirmation that the desired mechanism operates in man greatly enhances their utility. Manipulation of the relative potency of the constituents of a molecule with dual activity (or a combination drug regimen) may modify the desired outcome. The relatively high potency of the β2-agonist component of sibenadet is an interesting candidate to explain the surprisingly rapid loss of effect in the longer studies that mirrored the previously observed time course of therapy in their first 6 weeks. Such an explanation can, however, only be speculative at this time.

Symptoms can, and should, be quantified. The development of the BCSS illustrates how a relatively simple scale, using data that can be easily collected, can provide important clinical insights. The potential for using this approach in developing patient self-management plans is therefore apparent. By using symptom-based scales, such as the BCSS, the time course of exacerbations can be monitored and changes similar to those seen in more carefully controlled clinical cohort studies can be replicated (10). This has great potential for improving our understanding of these crucial events, but would require considerable investigation and definition before any clinical application could be realized.

The time course of most clinical events in COPD is slower than those of asthma. This does not simply apply to changes in pulmonary function, but is even more important when endpoints downstream from the purely physiologic are considered. Thus changes in health status reflect, in part, sustained changes in the intensity and frequency of the symptoms patients experience. Likewise, exacerbations must have a chance not to occur before their absence is slowly registered as an improvement in wellbeing. Having demonstrated proof of concept, clinical studies of new treatments would be best advised to adopt an assessment period of at least 12 weeks to capture some of these effects on wellbeing or exacerbations before committing patients, doctors and sponsors to longer and more taxing studies. The study period would, however, be largely dependent on the mechanism of drug action and anticipated outcomes.

Despite disappointing efficacy results, the development of sibenadet has provided additional information on drug design and evaluation that will prove a valuable resource for future investigation in this field. The creative solutions developed to address each challenge may pave the way for future agents, with the hope that better solutions can be found to improve therapeutic options for patients with COPD.

REFERENCES