TRENDS AND INNOVATIONS IN RESPIRATORY DRUG DEVELOPMENT

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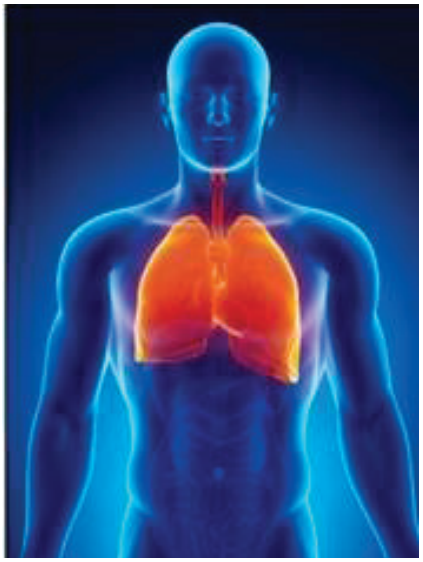
For years, the development of drugs for respiratory diseases, mainly asthma and chronic obstructive pulmonary disease (COPD), have been relying on the administration of a new drug, mostly by inhalation and assessment by physiologic tests and questionnaires. More and more these new drugs are administered in fixed combinations.



Adequate control of disease status and progression are still mostly assessed by lung function tests with a particular focus on forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). However, clinical and patient-reported outcomes, such as dyspnoea, exercise capacity, exacerbations, use of rescue medication, physical activity, health-related quality of life and mortality, have been applied more frequently as essential part of the clinical assessment.

Currently, the most frequently used lung function tests have a lack of sensitivity for patient-relevant clinical outcomes. Moreover, new insights in phenotype (defined by clinical features that distinguish between individuals), endotype (subtypes defined by distinct physiological mechanisms) of these diseases and in the basic mechanisms, combined with the discovery of new targets for therapy, have led to the need for a more personalized patient-centered approach and precision medicine.

Therefore, there is an unmet medical need for better outcomes and study designs in the development of treatments for respiratory diseases.

A. BETTER OUTCOMES

1. Outcomes in asthma trials

Minimal recommended outcomes for asthma trials, apart from respirometry pre- and postbronchodilator therapy, are symptom scores such as the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT). Exacerbations are measured by number of hospitalisations, emergency department visits, steroid and rescue medication use. Biomarkers are measured as total and allergen specific IgE (sIgE).

Alternative outcomes, already used before for diagnostic reasons and for phenotyping, have now increasingly been used as outcome parameters in clinical trials. Fractional exhaled nitric oxide (FENO) is an easy-to-measure, reproducible, non-invasive biomarker of inflammation.

Health-related quality of life (HRQOL) is a patient-related outcome used to assess the perceived burden of asthma. Quality of life questionnaires have been validated and compared. HRQOL considers not only the impact of asthma control and severity, but also the impact of comorbid conditions and the potential additional burden of treatment side effects.

Blood and sputum eosinophils and neutrophils, IgE, sIgE, periostin, another biomarker of inflammation, have been used to define inflammatory asthma phenotypes, as predictors of airway asthma exacerbations and as a potential target for anti-inflammatory biotherapies. Induced sputum cells and supernatant analysis is a noninvasive way to investigate airway inflammation that has been extensively used in cross-sectional and longitudinal studies. Apart from the inflammatory mediators, already mentioned, it allows the measurement of more specific cytokines like Il-4, Il-5, Il-6, Il-13, targeted by new therapies. Although there is still a lack of a golden standard for sputum induction and a quite elaborate and time-consuming sample handling, following a strict protocol and increasing experience has shown highly valid and reproducible data.

Furthermore, exhaled breath condensate (EBC) analysis of its components, such as airway pH or oxidative-related mediators, may assess airway

inflammation, although there are still problems of dilution repeatability and reproducibility that preclude their use in clinical trials. There is also a trend for the increased use of challenge agents, such as histamine, methacholine and endotoxine (LPS) to study the effect of drugs in asthma. Adequate use of allergen bronchoprovocation and, more recently, the use of the human viral challenge model, based on the developing insights in the viral triggers for asthma exacerbations, can help a more performant drug development.

2. Outcomes in COPD trials

According to the draft guidance of the FDA, the primary efficacy endpoints for a COPD trial should be improving airflow obstruction by demonstrating a change in post-dose FEV1 for a bronchodilator and change in pre-dose FEV1 for a nonbronchodilator. Other primary endpoints could be providing symptom relief, reflecting the claimed clinical benefit (e.g. reduce), modifying or preventing clinically meaningful measures of exacerbations, altering disease progression by the serial measurement of FEV1 over time and modifying lung structure by a sensitive radiological assessment of lung structure.

Commonly used secondary efficacy endpoints include clinically meaningful improvements in various measures of lung function, exercise capacity, symptom scores, activity scales, and health-related quality-of-life instruments. Biomarkers can, in some cases, also provide support of efficacy.

Although other outcomes like exhaled nitric oxide fraction (FeNO), Exhaled Breath Condensate (EBC), eosinophils in blood and (induced) sputum and other biomarkers have been more extensively studied in asthma, there is increasing interest in studies in COPD. The problem with these biomarkers, and also with some scales and (electronic) Patient-Reported Outcomes (ePRO), is proper validation before they can be generally accepted as outcomes in clinical trials by the authorities, especially when they are used as primary outcomes.

Because of a decline in approval rates for new drugs, high attrition rates and increasing costs, the pharmaceutical industry has a rising interest in quick wins, fast fails. One method of attempting to improve this is to focus on proof-of-concept studies. For inhalation drugs, the most frequently used method of drug administration in respiratory diseases, not only COPD, this could be done by studying lung deposition in humans and increased use of modeling and simulation techniques. This would enable leveraging of more classical outcomes from early pharmacokinetic and pharmadynamic studies to develop disease models that more appropriately predict the chances for success and failure.

As an example of this approach, SGS tested a biologic drug administered by oral inhalation in a Phase 1, single center, open label study to evaluate local and systemic pharmacokinetics in 44 healthy adult male volunteers. The results of the local PK data in bronchial alveolar lavage fluid (BALF), combined with systemic PK and pharmacodynamics data, could be successfully used in a modeling and simulation exercise to develop an adequate model to study the drug effects of a dose finding study in children.

3. Outcomes in rare pulmonary diseases

These diseases include mainly Idiopathic Pulmonary Fibrosis (IPF), Cystic fibrosis (CF), Pulmonary Arterial Hypertension (PAH). They represent a major health care burden in the developed world. Recently improved insight in mechanisms and genetics of disease is leading to the development of new targeted therapies. In clinical studies, the most commonly used outcomes, are still lung function (FEV1, FVC), pulmonary exacerbations, health-related quality of life. There are also an increasing number of validated biomarkers, patient reported outcomes, and imaging techniques. In many cases however, we are still struggling with evaluation of early stages and proof-of-concept studies.

So for the study of treatments for IPF, there is still an ongoing debate about selection of the optimal primary endpoint, whether it is all-cause mortality, progression-free survival (PFS), or Forced Vital Capacity (FVC).

In general, no single endpoint is suitable to all types of therapies and composite endpoints are used in many studies. In early phase studies, there is no clarity about outcomes, able to detect meaningful disease change. Exploratory omics-based research in populations of carefully phenotyped patients with IPF will hopefully lead to the identification of candidate outcome measures. Without such measures the drug development pipeline in IPF remains incomplete.

As secondary outcome parameters are used:

- Six Minute Walk Test (6MWT) and other physiologic outcomes
- Biomarkers
- As PRO, the St. George's Respiratory Questionnaire validated for IPF (SGRQ)
- Quantified high-resolution computed tomography (HRCT) scores
- Positron emission tomography (PET) scans

Additionally, in CF, for example, the Lung Clearance Index (LCI) based on multiple-breath inert gas washout (MBW) testing seems to be a valuable tool, that also can be used easily in infants. Also, the combination of CT and PET scan in fusion images, using fluorodeoxyglucose (FD) PET/CT is a useful tool for detecting inflammatory changes resulting from treatment for pulmonary exacerbations in pediatric patients with CF. These changes, correlated with lung function, sputum neutrophil counts, and CF-CT scores, quantified by using standardized uptake values (SUVs).

4. Leverage of lung function tests

One technique for improving the value of measuring respiratory function is body plethysmography. This allows assessment of long volumes, such as functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV). Also diffusion capacity can be measured with this technique by using dilutional gas methods.

Body plethysmography is safe and noninvasive, but requires certain equipment and skilled personnel. Therefore, body plethysmography is not usually performed in larger clinical trials. This is unfortunate because body plethysmography also allows

assessment of airway resistance (Raw) by the direct measurement. Raw is less dependent on patient effort compared with forced volumes and provides an assessment of airway caliber.

Another technique to assess pulmonary mechanics and Raw is the forced oscillation technique (FOT). FOT is a noninvasive test which provides unique information about lung mechanics that is not available from spirometry or body plethysmography, e.g. the mechanical impedance of the respiratory system and affected by lung inhomogeneity. FOT employs small amplitude pressure oscillations superimposed onto the normal breathing and, therefore, it is non-invasive and independent from performance of different respiratory maneuvers. Also, these measurements have been standardised.

A last technique for leverage of lung function parameters is modeling and simulation. In a Phase I, single-ascending dose, randomized, crossover trial, in 34 patients, classical FEV1 was used as the outcome parameter. Due to the large 'within-subject' variability, the analysis failed to detect a clear dose-response relationship. Development of a kinetic-pharmacodynamic (K-PD) model appropriately predicted the data and made extraction of dose-response information possible. The model improved signal-to-noise ratio of the efficacy signal, allowing the selection of doses for a subsequent dose-finding study.

5. Role of biomarkers

In the last decade, major advances have been made in the field of biomarker research in various lung diseases, including asthma, chronic obstructive pulmonary disease, lower respiratory tract infections, lung cancer and interstitial lung diseases. Multiple biomarkers have been implemented in the clinical practice of respiratory physicians. In parallel with the evolving field of personalised medicine, the number of clinical trials that utilise biomarkers is increasing every year. The concepts of biomarker-stratified patient selection and targeted therapy have been established and their efficiency successfully proven.

Eosinophil granulocytes are widely used in clinical trials as a biomarker for eosinophilic asthma and as indicators for the level of T-helper cell (Th) type 2 activation. Together with total and allergen specific IgE, eosinophil granulocytes, either in peripheral blood or in induced sputum are used as an inclusion criterion.

Eosinophil granulocytes serve also as a biomarker to allow an enrichment design study. A further widely used biomarker in asthma is the fraction of exhaled nitric oxide (FeNO). In inflammation, nitric oxide is produced by inducible nitric oxide synthases in different inflammatory cells, e.g. in eosinophil granulocytes. FeNO measurement is conducted in patients with suspected asthma, in monitoring of disease activity and to adjust treatment with inhaled corticosteroids. Periostin was introduced as a biomarker that is induced by IL-13 and produced by the bronchial epithelium. It can be used as a surrogate marker for T-helper cell type 2 (Th2) activity. In COPD blood eosinophils are also used as predictors of exacerbations, and copeptin as a marker for increased cardiovascular risk.

Although there is considerable interest in using biomarkers as surrogate markers for disease outcome, no pulmonary clinical trial has been published so far that has tested a biomarker as a primary end-point indicating disease progression. Omics technologies are expected to speed up discovery of and increase the number of biomarkers used in lung diseases and can be the key to opening the door to personalised medicine. However, advances in omics technologies have not been incorporated into current clinical trial design in pulmonary medicine. Integrating omics in our clinical trial designs will allow trialists to focus treatments on patients likely to respond and to identify clinically relevant surrogate outcome and drug effect biomarkers. When used longitudinally, such a biomarker may grade the patient's progress through a course of treatment. Biomarkers may also provide pharmacogenomic information, identifying which dose of a medication will be effective in a particular patient. The new paradigm suggests that current models for clinical trial design miss potentially efficacious medications since the stratification of patients does not account for subphenotypes or endophenotypes. Imaging a respiratory trial with drug and placebo showing no significant difference on the primary outcome of forced vital capacity (FVC). However peripheral blood mononuclear cells were collected from each patient at the beginning and at the end of the trial and subjected to gene expression profiling by microarray analysis of isolated RNA. If there is a group of patients with distinct patterns of biomarkers that cluster together at the far end of the distribution, showing a greatly improved pulmonary function, this suggests that the drug was effective in this subpopulation.

Another group of biomarkers are imaging biomarkers. Also, there the translation from bench to bedside lags behind. Quantitative computed tomography has been used in COPD, asthma, and Cystic Fibrosis. CT morphometry can be useful for the quantification of airway remodeling. Magnetic resonance imaging may identify abnormal heterogeneity by inhalation contrast. Molecular imaging methods (PET/CT) can demonstrate pulmonary neutrophilic activity as has been explained already.

One of the most promising techniques is certainly Functional Respiratory Imaging (FRI) combining high-resolution computed tomography (HRCT) imaging with advanced engineering to construct 3D biomarkers, using computational fluid dynamics. FRI has the unique capability of producing highly clinical relevant patient specific biomarkers, presenting 3D visualization of the patient's airway and lung geometry, regional airway resistance and aerosol deposition patterns.

For all types of biomarkers, validation and acceptance by regulatory authorities remains hard to achieve.

B. IMPROVEMENT IN DESIGN OF STUDIES

1. Adaptive trial design

The goal of adaptive trials is to increase the efficiency of randomized clinical trials, potentially benefiting trial subjects and patients with reduced cost and

enhanced likelihood of finding a true benefit of the therapy being studied. These designs can be used for exploratory and confirmatory clinical trials. The emphasis in exploratory clinical trials is on finding safe and effective doses, assigning a larger proportion of patients to treatments with a relevant effect, reducing the number of patients in groups with a poor effect, and to select the best doses for confirmatory trials.

In confirmatory trials, prospectively planned changes to the course of an ongoing trial are made based on an interim analysis of data, in a blinded or unblinded way, without undermining the statistical validity of the study. There are four major categories of adaptations:

1. Seamless phase 2–3 designs
2. Sample-size reestimation
3. Group sequential designs
4. Population-enrichment designs

An example of a Seamless Phase 2–3 Design is the Indacaterol to Help Achieve New COPD Treatment Excellence (INHANCE) trial. It was an adaptive two-stage, confirmatory, randomized clinical trial of several doses of inhaled indacaterol, a once-daily long-acting beta2-agonist for the treatment of COPD, in comparison with placebo, formoterol, or tiotropium.

Two of the four indacaterol doses were to be selected for further testing at stage 2 along with placebo and tiotropium. The final analysis would be based on the combined data from the two stages. The two most important statistical considerations for a design of this type are the dose-selection rule at the interim analysis and the statistical inference at the final analysis.

The dose selection must be made by an external data and safety monitoring comittee. This committee selected two doses for the second stage of the trial. The final analysis was performed when 285 additional patients had been enrolled and evaluated. The difference between each indacaterol dose and either placebo or tiotropium was significant with respect to the primary and key secondary end points.

This example shows several conditions that are essential for the successful implementation of an adaptive design. First, the highly quantitative, precise, and easily obtained early readout of end-point data made it possible to eliminate two of the trial groups quickly and enrol many more patients in study groups of primary interests. Second, the preliminary planning for this trial was meticulous, with detailed dose-selection criteria, a communication plan for disseminating interim results, a hypothesis-testing strategy that controlled the type I error, and detailed simulations of the operating characteristics before the initiation of the trial.

2. Decreased variability between multicentre sites

Variability between sites can be decreased in different ways by supporting site staff, using one type of equipment for measuring important outcomes, delivered by one vendor responsible for equipment and training of sites in the technique, electronic recording of data through one software system, using one set of standard operating procedures. Using SGS satellite's network, a sort of virtual monocentric site was created. This was based on the SGS clinical pharmacology unit know-how, expertise, services and procedures. This was combined with dedicated SGS clinical trial coordinators, study nurses, lab technicians, pharmacy support and training staff. Strongly motivated local hospital staff collaborated with SGS, driven by a hospital policy for strategic development.

3. Precision medicine

Precision or personalized medicine is an evolving field, in which treatments are tailored to the individual patient. Much of the current focus of precision medicine involves developing new drugs for personalized treatment of cancer and other diseases.

Increased attention to precision medicine has certainly emerged in scientific literature, lay press and public health. The announcement of the precision medicine initiative in the US has led to a variety of responses. The initiative aims to empower clinicians, patients, and investigators to work together toward more personalized care and improved clinical outcomes. It includes the development of a large patient cohort from which both clinical and "omics" data would be collected.

Enthusiasm about the field has been heightened by a rapid reduction in the cost of high-throughput genomic sequencing and a dramatic increase in the identification of potential molecular targets for therapy. Biomarker tests for

molecularly targeted therapies can help physicians to select the most effective therapy for a patient's condition and avoid treatments that could be ineffective or harmful.
If it is developed and maintained in a rigorous, evidence-based fashion with well-designed and well-executed studies, precision medicine could rapidly advance the care of patients by tailoring treatment to individual patients' conditions. This would improve clinical outcomes and quality of life, while reducing costs by averting the use of ineffective or harmful therapies.

One step forwards in the direction of precision medicine in asthma was shown recently in a study with dupilumab, a fully human anti-interleukin-4 receptor α monoclonal antibody, that inhibits interleukin-4 and interleukin-13 signalling, key drivers of type-2-mediated inflammation.

Adults with uncontrolled persistent asthma who are receiving medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist require additional treatment options as add-on therapy. In a andomized, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial, the efficacy and safety of dupilumab as an add-on therapy in 769 patients with uncontrolled persistent asthma was studied. Dupilumab increased lung function and reduced severe exacerbations irrespective of baseline eosinophil count and had a favourable safety profile.

4. Pragmatic trials:

Many current trials may not adequately inform practice because they were performed with relatively small sample sizes, at sites with experienced investigators and highly selected participants, overestimating benefits and underestimating harm. This leads to the belief that more pragmatic trials, designed to show the real-world effectiveness (RWE) of the treatment in broad patient groups, are required. Pragmatic trials require that participants be like patients who would receive the intervention if it became usual care.

One barrier to unselected participant recruitment however, is informed consent. To guarantee that everyone who is eligible is included, this requirement would need to be waived in some cases. A pragmatic approach is easier when an intervention is implemented at a group level rather than at an individual level. Cluster randomization, which involves groups of patients (in the same health care facility) who are randomly assigned to the same intervention, is popular in pragmatic trials.

Good trials also include a variety of investigators with a representative mix of experience appropriate to the intervention under study. Efforts that are made to minimize biases in open trials include focusing outcomes on major events, such as death and emergency hospital admissions. Pragmatic end points should also be important to patients, like symptoms, disability, and quality of life.

In a controlled effectiveness trial, the Salford Lung Study, conducted in 75 general practices, 2,799 patients with COPD were randomly assigned to a once-daily inhaled combination of fluticasone furoate at a dose of 100 µg and vilanterol at a dose of 25 µg (the fluticasone furoate-vilanterol group) or to usual care (the usual-care group).

The primary outcome was the rate of moderate or severe exacerbations among patients who had had an exacerbation within one year before the trial. Secondary outcomes were the rates of primary care contact and secondary care contact. The rate of moderate or severe exacerbations was significantly lower by 8.4%. There was no significant difference in the annual rate of COPD-related contacts to primary or secondary care.

The strength of the trial derives from its innovative design. It took place in a single urban area, with primary and secondary care connected through an EHR, integrated with a new data recording system to enable the collection of a trial-relevant data set. All treatment was carried out by the usual care-givers, while patients were simultaneously monitored remotely with the use of the EHR for the early detection of safety events.

Collecting real-world evidence for external validation is driven by an increase of the patient-centric approach. Along these lines, there is also an increasing use of outcomes relevant to patients, and patient engagement. The use of Big Data, derived from EHR and large registries, linked to integrate RWE adds to this approach. Also, the collection of outcome data through the use of patient's own devices (Bring Your Own Device - BYOD), electronic Patient Reported Outcomes (ePRO) and electronic Clinical Outcome Assessment (eCOA) are helpful in realizing the goal of outcomes that matters to patients and patient engagement.

CONCLUSION

We can conclude that there exists a low performance of classical primary respiratory endpoints in exploratory and confirmatory studies, showing a lack of sensitivity for patient-relevant clinical outcomes. So, there is a high need for more sensitive outcomes in respiratory drug development. In recent years, a great number of emerging new and existing techniques has been put forward, but further validation is needed before they can be accepted generally, certainly as primary outcome parameters in randomized trials. Until now, they demonstrated most value in translational and exploratory development.

There is a clear need to extend these findings to confirmatory trials, and to apply them in the collection of real-world evidence. The need for a patient-centric approach through all stages of clinical development is becoming mandatory. So, an evolution from classical randomized clinical trials with low external validity and delays, which will be remain necessary for regulatory submission, to more efficient and adaptive designs will be seen in the future.

An evolution from undefined targets to a more targeted approach will lead us closer to precision medicine. Finally, clinical research in general will move from a researcher-centric approach to a patient-centric approach.

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