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1. REGULAR VERSUS AS-NEEDED TREATMENT OF ASTHMA

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Asthma management guidelines have identified the primary goal of management is to achieve asthma control. Asthma control consists of optimizing current (day-to-day) control and minimizing future risk defined by long term decline in lung function, severe asthma exacerbations and unwanted effects from medications. The more poorly controlled day-to-day asthma is, the greater the risk of a severe asthma exacerbation.

Despite the availability of effective and safe medications to treat asthma, the most important of which are inhaled corticosteroids (ICS), either alone or in combination with long-acting inhaled β_2-agonists (LABA), many patients remain poorly controlled.[1] The most important reason for this is poor adherence and persistence with maintenance treatment.[2] This results in many patients using short-acting inhaled β_2-agonists (SABA), as needed, as their only treatment option.[3] SABAs have no anti-inflammatory properties and, in some circumstances, can enhance eosinophilic airway inflammation in asthmatic airways.[4] This has been shown to increase future risk in asthma and overuse of SABAs increases risk of asthma mortality.[5]

The use of combination of an inhaled corticosteroid (ICS) and a rapid-onset long-acting inhaled β2-agonist (LABA) reduces exacerbation risk in patients whose asthma is not controlled by ICS alone,[6] and this is further reduced when the combination of the ICS budesonide LABA formoterol is used both as a maintenance and reliever treatment in these patients.[7] In addition, in patients with milder asthma, using a combination inhaled containing both a SABA and an ICS has been demonstrated to reduce asthma exacerbation risk when compared to a SABA as reliever.[8]

More recently, a series of studies, in patients who require daily maintenance ICS, has compared a combination inhaled containing an ICS and the rapid onset LABA as-needed, formoterol, to daily maintenance ICS, and to a SABA as-needed,[9,10] or to ICS maintenance as the only comparator.[11,12] These studies have consistently demonstrated the use of the ICS/formoterol as-needed reduces severe asthma exacerbation risk by at least 60% when compared to SABA as-needed, and is at least comparable to ICS maintenance in reducing exacerbation risk. Maintenance ICS is slightly better than as-needed ICS/formoterol in improving pre-bronchodilator FEV_1 and the asthma control questionnaire (ACQ). However, this required a much higher average daily dose of ICS and regular twice daily treatment.

These studies have consistently demonstrated that ICS/formoterol combination is better than SABAs as a reliever treatment in asthma of all severities. Maintenance ICS remains the optimal treatment choice for patients with mild asthma, but because of very high rates of poor adherence to ICS maintenance, as-needed ICS/formoterol should also be considered as a treatment option for mild asthma patients.

Conflict of interest

Paul O'Byrne has received consulting and/or speakers fees from AstraZeneca, GSK, Chiesi, Menarini, and grants-in aid from AstraZeneca, Bayer, Medimmune, Novartis, Merck.

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2. CAN LUNG CANCER BE CURED? THE ROLE OF IMMUNOTHERAPY IN NON-SMALL-CELL LUNG CANCER

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According to the most recent annual statistics report from the American Cancer Society,[1] the death rate from cancer in the US has declined steadily over the past 25 years. Lung cancer represents the biggest driver of this declining trend—though remaining the top cause of cancer-related deaths—, lowering the age-adjusted death rate by 48% in men and by 23% in women, a trend which has been accelerating in recent years. Reasons underlying this decline might be a result of the steady reduction in smoking over the last decade and from the introduction of early detection programs, however, it is at least conceivable to consider that progress in treatments—especially through the introduction of targeted therapies and immunotherapy—may be the most significant reason for this success.

For decades, treatment for lung cancer continued to be based on platinum-based chemotherapy. But its efficacy, in terms of outcomes, remained on a plateau. A significant step forward came through the development of targeted therapies and the reliance on predictive biomarkers to identify those individuals deriving the greatest therapeutic benefit. A better genomic characterization of non-small-cell lung cancer (NSCLC)[2] enabled us to pinpoint a number of genetic drivers of tumor growth—such as *EGFR, ALK, ROS, and BRAF*—and paved the way for the development of targeted therapies whose use is currently approved based on their survival advantage over chemotherapy.[3] But the future looks even brighter, and novel, promising agents targeting other actionable biomarkers such as *NTRK*, *RET, METex14, HER2*, and even the "untargetable" *KRAS* might soon broaden the repertoire of personalized therapies in NSCLC. We are certainly living in exciting times, but significant challenges remain in overcoming drug resistances or promoting equal access to broad genomic profiling in clinics.

Beyond any doubt, immunotherapy is another unprecedented advance that has transformed the treatment landscape for NSCLC, generating increasing optimism and hope among the scientific community and patients. Unlike chemotherapy or targeted therapies, immunotherapy drugs indirectly attack tumors, by inducing a host immune-response through inhibition of particular proteins—such as PD-1 or PD-L1—that stop immune cells from recognizing tumors. Several trials with immunotherapy have already demonstrated very encouraging results and significant activity in lung cancer. Indeed, treatment with immunotherapy, either alone or in combination with chemotherapy, has reset the standards and is now considered a "must" in the forefront treatment of all advanced NSCLC patients without oncogenic drivers.[4] Although immunotherapy does not work for all patients, it can achieve long-term and durable responses with good quality of life in a subset of patients[5] and each year we eagerly await the clinical trial updates in the hope that, with longer follow-up, we will be able to maintain the long-term survival plateau above 16%—for a disease in which the expected five-year survival was less than 5%.

But the benefits of immunotherapy extend beyond advanced disease. Adding one-year consolidation immunotherapy after radiation and chemotherapy has demonstrated encouraging improvements in survival in patients with locally advanced NSCLC, setting a new standard of care for the treatment of stage III unresectable NSCLC.[6]

Based on the success of immunotherapy in locally/advanced disease, the next reasonable step is to determine whether the immunotherapy benefit can be translated earlier in the disease course, by reducing systemic recurrences and improving cure rates. In this respect, a large number of pivotal, neoadjuvant and adjuvant trials of immunotherapy alone or in combination with chemotherapy are now in progress.[7] The preliminary promising results of some of these exploratory trials with immunotherapy—mainly in the neoadjuvant setting[8]—anticipate exciting times ahead in the curative treatment of early stage NSCLC and, if confirmed, could change the treatment landscape of NSCLC as a whole.

Conflict of interest

In the last 5 years, Dr. Reguart has received speaker's honoraria for speaking at sponsored meetings from MSD, BMS, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, Abbvie, Ipsen, Novartis, Astrazeneca, Lilly, Takeda, Amgem, and payments for organizing educational events from Amgem, Roche. She has received honoraria for attending advisory panels from MSD, BMS, Roche, Boehringer Ingelheim, Guardant Health, Pfizer, Abbvie, Ipsen, Novartis, Astrazeneca, Lilly, Takeda, Amgem. She has also received sponsorship to attend international scientific meetings from Boehringer Ingelheim, MSD, and Roche. She has received research grants from Novartis and Pfizer.

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3. CURRENT MANAGEMENT OF CHRONIC COUGH

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Chronic cough can be a consequence of many pulmonary and some non-pulmonary conditions.[1] Most will be readily apparent after a simple clinical assessment, including a physical examination, chest radiograph and spirometry. Cough that remains unexplained after such an assessment is a common reason for referral to secondary care, accounting for up to 10% of new referrals to a respiratory clinic.[2] Guidelines emphasise the importance of asthma and other eosinophilic airway diseases, gastrooesophageal reflux disease and upper airway conditions[3,4] but these recommendations are based more on expert opinion than on high quality evidence. There is increasing recognition that satisfactory control of chronic cough is not achieved in a significant proportion of patients and that there is a significant unmet need for better anti-tussive treatments.[2,4] I will suggest that factors potentially associated with non-asthmatic cough are viewed either as potential pathophysiological cause or as aggravating factors of the abnormality of the cough reflex rather than the cause. Eosinophilic airway inflammation, smoking and ACE-inhibitor therapy are important causes of the former and gastroesophageal reflux and rhinitis potential causes of the latter. The clinical impact of removing a potential cause of heightened cough reflex is likely to be large whereas the effect of removing an aggravating factor will depend on the extent to which the primary abnormality of the cough reflex is the dominant problem.[2] I will outline an approach to the clinical assessment of a patient with an isolated chronic cough.

I will review progress that has been made in the assessment of chronic cough.[5,6] This has highlighted a heightened cough reflex as a potential treatable trait in patients with airways disease. In recent years there has been significant progress in the development of new treatments for a heightened cough reflex with the discovery that antagonism of the extracellular purinergic receptor P2X3 with gefapixant results in a significant reduction in cough frequency, reduction in cough reflex sensitivity and improvement in cough related quality of life.[7,8] Research into the basic mechanisms and pharmacological control of a heightened cough reflex is likely to identify new treatment targets in the coming years.

Conflict of interest

In the last 5 years, Ian Pavord has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Inglehiem, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini and GSK and payments for organising educational events from AZ, GSK, Sanofi/Regeneron and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca, Teva and Chiesi. He has received a grant from Chiesi to support a phase 2 clinical trial in Oxford. He is co-patent holder of the rights to the Leicester Cough Questionnaire and has received payments for its use in clinical trials from Merck, Bayer and Insmed. In 2014–2015 he was an expert witness for a patent dispute involving Astra Zeneca and Teva.

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4. RADIOMICS: IMAGE AND ARTIFICIAL INTELLIGENCE GOING HAND IN HAND

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Artificial Intelligence (AI) is one of the areas that has experienced the fastest growth in recent years and with great relevance in radiology. A recent PubMed search for the term "Artificial Intelligence" found 82,066 publications and when AI was combined with "Radiology" 5405 articles appeared, most of these articles have been published from 2005.

Machine learning allows computers to learn from data and reproduce human interpretations without being explicitly programmed. Related to machine learning is the computational imaging that makes it possible for machines to analyze, process and understand images by performing tasks that human vision cannot do. These systems can detect, segment and classify medical images and, with the application of deep learning, do so unsupervised and continuously learning. It is estimated that AI may have an impact, in addition to the classic image interpretation, on: radiomics, imaging biobanks, clinical decision support systems, structured reports and workflow.

Thoracic imaging is a field with great potential for the development of AI-based applications. It can be applied on chest radiographs, one of the procedures with the highest volume, often not reported or with errors of detection due to low contrast or overlapping of bone structures. AI systems or computer-aided detection (CAD) systems have been designed for the automatic assessment of radiographs or to assist the radiological report. In the same way, in the field of computed tomography, AI has special application and interest in the detection and evaluation of the pulmonary nodule, and in assisting the screening of lung cancer with low dose CT. Other pathologies where AI is being applied are the assessment of diffuse interstitial diseases and emphysema. Based on deep learning techniques and convolutional neural networks, it has been possible to match or exceed the performance of radiologists in the classification of pulmonary nodules or fibrotic lungs.

A further advance of AI is to move from detecting, segmenting and classifying to characterize and predict, this is what radiomics achieves. Radiomics consists in the extraction of a large number of quantitative imaging features from standard-of-care medical images. These features are not detectable by the human eye. Imaging features are analyzed and modelled to exploit them with data mining, with the aim of predicting a specific parameter, whether prognosis, histological diagnosis or response to treatment. A special type of radiomics is radiogenomics, which tries to find relationships between the image features and tumor genetic signatures.

Radiomics in pulmonary pathology has been applied especially in the field of oncology and lung cancer screening, but its use is extending to diffuse parenchymal pathologies.

The great limitation of radiomics is the variability, reproducibility and generalization of its results. A recent study evaluating 77 studies in which radiomics was used in 2018 concludes that the overall scientific quality of the studies is insufficient, and they must improve their reproducibility and clinical application.

AI and radiology are very promising techniques for the non-invasive evaluation of multiple lung pathologies, but their application in routine clinical practice is not ready, being necessary prospective studies and in real situations.

Conflict of interest

In the last 5 years, Dr. Sánchez has received speaker's honoraria for speaking at sponsored meetings from BMS, Roche, Boehringer Ingelheim, Lilly and Menarini. He has also received sponsorship to attend international scientific meetings from General electric and Siemens. None of these are related to the subject of the work.

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5. BREATHOMICS IN LUNG DISEASES

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The management of chronic lung diseases, such asthma, COPD, lung cancer and others requires the phenotyping of individual patients in order to tailor existing and newly developed treatments.[1] Clinical phenotyping does not suffice anymore as cellular and molecular measurements are essential for biological subtyping of a diseased state in individual patients at a particular point in time. To that end several molecular platforms are being used, varying from transcriptomics, proteomics to metabolomics.[2] In order to be applicable for repeated measurements in daily clinical practice such platforms should not only be accurate and reliable, but also non-invasive, rapid and cheap. Breathomics using volatile organic compounds (VOCs) in exhaled air increasingly meets these requirements.[3]

Exhaled VOCs can be identified by gas chromatography and mass spectrometry (GC-MS), which is required for pathophysiological research.[4] Electronic nose (eNose) technology using cross-reactive sensors and pattern recognition algorithms merely recognizes complex VOC-mixtures, but does provide probabilistic information that is suitable for clinical decision making.[4] The latest generation of eNoses has been designed and validated for usage in clinical practice, including exchangeable hardware, online quality control and pseudo real-time computing in a large data cloud (for instance:

www.breathomix.com). This allows presentation of the results at point of care, thereby supporting disease management decisions whilst the patient is still in the doctor's office.

eNose assessment of exhaled air shows high diagnostic accuracy amongst asthma, COPD and lung cancer.[3] Interestingly, this also includes high predictive values of the prospective development of lung cancer amongst COPD patients. The efficacy of immunotherapy with checkpoint inhibitors can be predicted by eNose at the start of therapy with better accuracy than any other existing biomarker.[5] eNose is also providing phenotypic information on inflammatory profiles (eosinophilic, neutrophilic) in asthma and COPD[6,7] and on the presence of an exacerbation.[8,9,10] Preliminary evidence suggests that this also holds for predicting therapeutic responsiveness (to steroids and anti-IL-5).

The present data demonstrate that pattern recognition of exhaled VOCs by eNose qualifies for rapid phenotyping of patients with asthma, COPD and lung cancer at point of care. If needed, in parallel GC-MS might link the key VOCs of these breathprints to contributing pathobiological pathways.

Conflict of interest

Peter Sterk is scientific advisor and has a formally inconsiderable interest in the start-up company Breathomix BV.

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6. BRONCHOSCOPIC LUNG VOLUME REDUCTION: VALVES VS. COILS AND OTHER DEVICES

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A key consequence of COPD is hyperinflation which leads to increased breathlessness, reduced exercise performance, impaired quality of life, hospitalization, respiratory failure and even death.[1,2] This is especially important in patients with COPD that have an emphysematous predominant component to their disease. Therapies that reduce hyperinflation may improve outcomes. In the National Emphysema Treatment Trial (NETT) lung volume reduction surgery (LVRS) improved lung function, exercise performance, quality of life and in a subset of patients with upper lobe predominate emphysema and ventilatory limitation during exercise, survival.[3] However, LVRS is associated with a 4.3% mortality at 90 days in the most optimal LVRS patient candidate and also has substantial cardiorespiratory morbidity.[4]

Because of the increased morbidity and mortality associated with LVRS, less invasive bronchoscopic approaches to lung reduction have been examined. These include a variety of bronchoscopic procedures that aim to decrease thoracic volume to improve lung, chest wall and respiratory muscle mechanics.

The bronchoscopic procedures breakdown into three distinct categories: (1) targeted lobe atelectasis (endobronchial valves and lung coils); (2) destruction and remodeling of emphysematous tissue (flowable sclerosing and adhesive agents) and, (3) bypass tract stenting or transpleural ventilation (endobronchial stents or externally placed modified chest or gastrostomy tubes).

All the above therapies have been subjected to clinical trials with reported successes and failures. Prospective studies have shown that the use of endobronchial stents are not effective.[5] Pilot studies of transpleural ventilation using external devices failed due to inability to maintain patency and increased patient morbidity. A multi-center study using a lung sealant was discontinued prematurely. While the study reported significant benefits in some physiologic parameters, the intervention had unacceptably high morbidity and mortality.[6]

The first large prospective multicenter RCT of endobronchial valve (EBV) placement showed statistically significant improvements in FEV_1 and 6-minute walk distance at 6 months post intervention but the magnitude of the observed improvements was not clinically meaningful.[7] However, approximately 30% of EBV treated subjects did experience statistically significant and clinically meaningful benefit. Features that identified clinical benefit were the presence of an intact fissure, greater emphysema in the targeted treated lobe compared to the ipsilateral non-treated lobe of at least 15% and an upper lobe location. However, on multivariate analysis, only the presence of an intact fissure was statistically important indicating a fourfold greater likelihood of treatment benefit.[8] Fissure integrity has been assessed using structural analysis based on high-resolution Chest CT images (HRCT), as well as physiological assessment of flow across the fissure using a balloon tipped catheter inserted into the targeted lobe.

Additional prospective clinical studies in patients with heterogeneous, or heterogeneous and homogenous emphysema were performed using fissure integrity as a criterion for enrollment.

Non-significant increases in median FEV_1 at three months post valve implantation in one study was attributed to EBV placement in some patients despite collateral ventilation.[9] Another study showed significant increases in FEV_1 and 6-minute walk distance in subjects without collateral ventilation compared to controls at 6 months.[10] Adverse effects in the EBV treated group in both studies included pneumothorax, and EBV removal or replacement.[9,10] In all studies, greater benefit was shown in patents with heterogeneous emphysema compared to a homogenous pattern.[10]

A large multicenter, prospective, RCT of EBV treatment in patients with heterogeneous emphysema distribution and little to no collateral ventilation, demonstrated significant clinically meaningful benefits over usual care in lung function, dyspnea, exercise capacity, and quality of life out to at least 12-months post-procedure.[11] Pneumothorax was seen in 26.6% of subjects treated with the EBV usually within the first 72 h of the procedure (76%). Another large multicenter prospective RCT using a different type of EBV in patients selected for targeted lobe treatment based on fissure integrity assessed by high resolution chest CT showed a significant between-group increase in mean FEV_1 from baseline (0.101L) and a 25.7% between-group difference in FEV_1 responder rates (improvement $\geq$15%).[12] These results persisted at 12 months. The EBV treated group also had significant reductions in hyperinflation and dyspnea. Improved health status and quality of life was also observed. Consistent with prior studies, pneumothorax occurred in 25.5% of EBV treated patients; the majority occurred in the first three days following the procedure during the period of average hospitalization.

Early-onset pneumothorax in the EBV treatment group likely results from lung conformation changes due to acute volume reduction in the emphysematous targeted lobe by valve therapy that triggers rapid ipsilateral non-targeted lobe expansion, a recognized indicator of successful target lobe occlusion in patients with intact fissures or absence of collateral ventilation. The occurrence of pneumothorax highlights the need for physicians performing this procedure to have expertise in managing procedural complications. After the post procedural period, however, patients treated with the EBV compared to usual care trended to less exacerbations and episodes of respiratory failure. A comparison of treatment benefits and complications associated with EBV placement compared to LVRS show comparable benefits with EBV treatment but with less complications.[11]

EBV have also been evaluated in patients with solely homogenous emphysema. An RCT of EBV treatment compared with usual care in patients with homogenous emphysematous without collateral ventilation reported improvements in FEV_1, 6 min walk distance and quality of life at 6 months with targeted lobe reduction in 97% of subjects as measured by volumetric CT.[13]

Unfortunately, EBV is not effective in patients that lack fissure integrity or exhibit collateral ventilation. Approximately 60% of hyperinflated patients with emphysema fall into this category.

Other bronchoscopic lung volume reduction techniques that do not depend upon intact fissures or absence of collateral ventilation have been studied.

In a prospective RCT, targeted thermal ablation of more diseased segments produced clinically meaningful and statistically significant improvements in lung function and health status at 6 months.[14] COPD exacerbation was the most common serious adverse event. Durability of these changes were subsequently repoted at 12 months follow-up.[14,15]

Two multicenter trials studied the effects of nitinol coils implanted into the lung compared to usual care on changes in 6-min walk distance, lung function and health status in patients with advanced homogenous or heterogeneous emphysema. Both studies reported increases in 6 min walk distance with coil treatment compared to control and smaller improvements in FEV_1, and quality of life measured by St George's Respiratory Questionnaire.[16,17] A subanalysis of one of the studies (RENEW) suggested that patients that had a residual volume >200% with absence of airways disease and coil placement in the lobe most destroyed by emphysema had better clinical outcomes.[18] Major complications in the coil group included pneumonia, pneumothorax, hemoptysis and more frequent exacerbations.

Overall, in patients with advanced emphysema and hyperinflation selected for fissure integrity (FI) or lack of collateral ventilation (CV), bronchoscopic lung volume reduction with endobronchial valve placement and total lobar occlusion can achieve clinically significant and durable improvements in lung function, dyspnea, exercise tolerance and quality of life. Future work needs to refine patient selection to improve outcomes, reduce complications, improve the procedural performance and to develop effective therapies for patients who lack fissure integrity or exhibit collateral ventilation positive status.

Conflict of interest

Gerard J. Criner reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, CSA Medical, Eolo Medical, Gala Therapeutics, GlaxoSmithKline, Helios Medical, Merck, Medtronic, Mereo BioPharma, NGM Biopharmaceuticals, Novartis, Olympus, PulmonX, Philips Respironics Inc, Respivant Sciences, The Implementation Group and Verona Pharma and has ownership Interest in HGE Health Care Solutions.

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7. STEM CELL THERAPY IN LUNG DISEASES: REALITY OR FICTION?

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In the 1970s, Friedenstein et al. discovered that bone marrow contained not only hematopoietic stem cells but also a small population of plastic adherent cells, which would later become known as Mesenchymal Stem Cells (MSCs).[1–3] Recently these cells have been isolated from a variety of tissues, including adipose tissue,[4] skeletal muscle,[5] synovium,[6] thymus,[7] lung,[8] and amniotic fluid.[9] MSCs have several unique qualities exhibiting immunomodulatory effects by secreting anti-inflammatory cytokines and growth factors, that make them promising therapeutic option to treat acute and chronic lung diseases.[10–12]

Chronic Obstructive Pulmonary Disease: Because of the protective abilities through the suppression of inflammatory cytokines and the production of growth factors, MSCs have a high potential for COPD. Like other chronic lung diseases, no animal models have shown to mimic the COPD found in humans accurately. The smoke-induced model of COPD appears to bear the closest resemblance to the human disease. Schweizer, et al. were the first to demonstrate the reparative effects of mesenchymal stem cells in smoke-induced murine models of emphysema. They exposed mice to smoke for 24 weeks before administering MSCs. Mice exposed to cigarette smoke without treatment showed severe alveolar destruction after six months of exposure that continued even after cessation. Mice treated with MSCs after exposure exhibited restored alveolar architecture two months after treatment and reduced the mean linear intercept (MLI) nearly to the control level.

There are two recently completed clinical trial evaluating the safety and efficacy of MSCs in the treatment of COPD. In the most extensive, sixty-two patients with moderate to severe COPD received either four monthly infusions of 100×10^6 allogeneic MSCs or a placebo. The patients were followed for two years after the first infusion. During the study, no adverse events were reported, and no increase in the frequency of exacerbations was observed. No significant changes in pulmonary function detected during this study. Based on these results, the administration of MSCs in patients with moderate to severe COPD appears to be safe.[13]

Idiopathic Pulmonary Fibrosis: In numerous animal models of experimental pulmonary fibrosis, MSCs have to exert a protective effect by ameliorating inflammation and reducing the degree of injury and fibrosis. While there are no models that are exact in mimicking idiopathic pulmonary fibrosis (IPF), the bleomycin model is the most widely used. Ortiz et al. were the first to report the protective effect of MSCs. They found that MSCs reduced collagen deposition in lung tissue, as well as limit the progression of fibrosis. Based on this and similar observations, there are currently several ongoing and two recently completed clinical trials, according to clinicaltrials.gov, concerning the safety and efficacy of MSCs in the treatment of IPF. The Prince Charles Hospital established the feasibility and safety of intravenous MSC administration in IPF patients. The patients were observed for six months. At the end of the study, only minor adverse events were reported, and there was no evidence of worsening fibrosis. A second study, conducted by Dr. Glassberg at the University of Miami, ended with a similar conclusion. In any of those trials, there was no demonstrated improvement in the clinical conditions of the patients.[14]

Acute Lung Injury: Acute respiratory distress syndrome (ARDS) is a devastating lung condition. Currently, it is the leading cause of death and disability in acutely critically ill patients, with a mortality rate that ranges between 26–50%. ARDS is an inflammatory state; Since the initial description, by our group, demonstrating protection in animal models of LPS-induced lung injury model, ARDS therapy with MSCs, is a promising therapeutic option for patients with ARDS. Two clinical trials have been completed. In the first trial, under M. Matthay direction, a multi-center, open-label, dose-escalation phase of a single dose of intravenous MSCs in patients with moderate-to-severe ARDS. A single intravenous infusion of a single infusion of allogeneic MSCs was well tolerated in 60 patients. None experienced any of the predefined MSC-related hemodynamic or respiratory adverse events. However, there was no protective effect by MSCs.[15] Recently an international effort involving several institutions in the United States and the United Kingdom complete a phase II clinical trial, demonstrating protection on several clinical parameters including days in the ICU, free ventilator days, and a decrease in mortality.

In summary, the use of MSCs on lung diseases still controversial. Completed clinical trials had demonstrated the safety of their use. However, protection still elusive, particularly for chronic lung diseases like COPD and IPF. A recent clinical trial on patients with moderate and severe ARDS demonstrates some level of protection, generating a moderate level of optimism.

Conflict of interest

Mauricio Rojas reports no conflict of interest with the data included in the presentation.

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