RESCUE STUDY: BURDEN OF RSV An Observational Study to Assess Respiratory Syncytial Virus (RSV)-associated Illness in Adults With Chronic Obstructive Pulmonary Disease (COPD)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON45338

Source
ToetsingOnline

Brief title
RESCUE Study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: COPD, Exacerbation, RSV, Susceptibility

Outcome measures

Primary outcome

The primary objective of this prospective observational study is to determine the incidence of RSV acute respiratory infection or events leading to worsening cardiorespiratory status across multiple consecutive RSV. In addition, we will assess if and how the occurrence of an RSV virus infection affects the long-term outcome of COPD as reflected by rate of lung function decline, course of symptoms, and rate of COPD exacerbations during the follow-up of this study.

Secondary outcome

As a secondary objective, we will investigate whether it is possible to predict the long-term outcome of COPD, occurrence of COPD exacerbations and vulnerability to develop viral infections including RSV. To this end, we will analyse clinical data as well as markers of mucosal immunity and gene expression. The following parameters will be assessed:

- Lung function (PEF, FEV1, FEV1/FVC, FVC, FEF25-75%).
- Daily PEF monitoring and symptoms recordings.
- IOS measurements, R5, R10, R15, R20, R5-R20, Fres, X5, AX.
- Multiple Breath Nitrogen Washout.

- In- and expiratory HRCT scan will be performed at baseline.

- PExA measurement will be performed at baseline.

- Questionnaires (health status [CCQ and SGRQ] and CAT).

- Blood transcriptomics for genetic susceptibility.

- Blood RSV serology.

- Blood cell differential counts.

- Frozen whole blood.

- Peripheral blood mononuclear cells for innate immune response.

- Spontaneous sputum for viral RT-PCR, inflammatory cell counts, inflammatory

cytokine release and bacteriology.

- Nasopharyngeal swab for virus detection.

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide and its morbidity and mortality are still rising. The WHO predicts that COPD will become the fourth leading cause of death worldwide by 2030

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The main pathologic features of COPD include tissue remodelling in the small airways (fibrosis and smooth muscle hypertrophy) and tissue destruction in the lung leading to emphysema. The first signs of COPD are often chronic cough, increased sputum production, and dyspnea. The presence and severity of COPD is generally documented by a decrease in FEV1 compared to the predicted FEV1 and a decreased FEV1/FVC ratio that is not or only little reversible by an inhaled bronchodilator. In addition, air trapping is present in a considerable proportion of COPD patients, as reflected by an increased

RV%TLC. This trapped air, i.e. hyperinflation, contributes to the dyspnea intensity that is experienced by COPD patients.

Exacerbations are regarded as important events for COPD prognosis, since an increased frequency of these episodes may hasten disease progression by accelerated decline in lung function and increased mortality rates, particularly if these require a hospital admission. The mechanisms by which exacerbations lead to progressive loss of lung function are not yet unknown. However, it is likely due to effects of acute inflammation and associated lung tissue damage. Of interest, the Cosmic study showed that symptoms persist for several weeks after an exacerbation, suggesting that underlying pathophysiology is not resolved with a two-week course of oral corticosteroids or antibiotics. It may thus be of importance to attack the ongoing inflammation with appropriate treatment at the appropriate location in the lungs.

Viruses that are commonly associated with acute exacerbations in COPD patients include influenza viruses, picornaviruses, coronaviruses, and paramyxoviruses. Most of the published studies to date have involved small study populations, and the percentage of illnesses caused by RSV in persons with COPD ranges widely from 0% to 17.4%. Though the percentage of illnesses caused by RSV shows a wide range, RSV has been nevertheless recognized as an important cause of COPD exacerbations

Human respiratory syncytial virus (RSV) causes severe disease in the very young, elderly and in high-risk groups. It has been estimated that RSV was associated with 34 million cases of acute lower respiratory tract infection (ALRI), 3.4 million ALRI hospitalisations and 55,000 to 199,000 deaths in children <5 years in 2005. These estimates are based on limited data and there is a substantial gap in knowledge (on morbidity and associated healthcare and social costs) across Europe. RSV infection in childhood is associated with subsequent wheezing and asthma. These long-term sequelae pose a substantial additional burden on the healthcare system. In addition, RSV is a significant cause of ALRI morbidity in elderly and COPD patients. Most published data on RSV disease burden in the elderly are from the United States and from hospital settings. The knowledge gaps have an impact on Europe*s ability to make evidence-based decisions nationally about novel vaccines and therapeutics. There is a parallel need to assemble clinical resources to identify correlates of severe RSV disease for clinical management, classification of disease severity in clinical trials and identification of biomarkers for severe disease.

COPD has been traditionally considered a self-inflicted disease induced by tobacco smoking. In healthy subjects, lung function declines physiologically with age. By contrast, the traditional pathophysiological paradigm of COPD proposed by Fletcher and Peto in the late seventies states that, COPD develops in the so called *susceptible* individuals because smoking enhances the physiological decline of lung function through life [18]. Recent research, however, has challenged this traditional paradigm by showing that an enhanced

decline of lung function occurs only in half of the COPD patients whereas the other half develop COPD because of poor lung function development early in life. Potential causes of poor lung development are multiple and include genetic and epigenetic factors, associated with environmental exposures such as, poor diet, repeated lung infections in infancy, passive smoking and/or prematurity. It is likely that the driving biological mechanisms vary between these conditions, thereby making COPD the common clinical endpoint of diverse molecular pathologies. In any case, this new concept has fundamental implications for the understanding of COPD, since it allows a novel stratification of patients based on their lung function trajectories that may be highly relevant for their individualized management. It provides the opportunity to treat or even prevent COPD with tailored interventions, targeting specific molecular networks operating in (innate and acquired) immunity, inflammation and remodelling. This study will aim to identify patients who are more susceptible to viral exacerbations with the potential to develop further treatments to prevent RSV exacerbations.

Study objective

The primary objective of this prospective observational study is to determine the incidence of RSV disease and document resource utilization in patients with COPD. In addition, we will assess if and how the occurrence of an RSV virus infection affects the long-term outcome of COPD as reflected by rate of lung function decline, course of symptoms, and rate of COPD exacerbations during the follow-up of this study.

As a secondary objective, we will investigate whether it is possible to predict the long-term outcome of COPD, occurrence of COPD exacerbations and susceptibility to respiratory viral infections including RSV. To this end, we will analyse clinical data as well as GWAS in blood and genome-wide gene expression in brushed nasal epithelium.

Study design

This is a prospective, observational study conducted across three consecutive RSV seasons to determine the incidence of RSV disease and document the incident rate of ALRI*s and COPD exacerbations in patients with COPD. Clinically stable subjects with COPD (i.e. Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage I-IV will be enrolled and followed for three years. At baseline, subjects will be more extensively characterized with a full medical history, lung function, blood for transcriptomics, nasal mucosal sampling, body plethysmography, multiple breath nitrogen washout (MBNW), blood and sputum cell differential, HRCT, and particles in exhaled air (PExA). Subjects will have twice yearly scheduled visits to obtain blood, nasopharyngeal swab, sputum, and clinical data and perform a spirometry. One visit will be scheduled before the RSV season (in the months between May and October), and one visit will be

scheduled during the RSV season (between October and April). In addition, unscheduled visits to collect blood, nasopharyngeal swab, sputum, and clinical data will be conducted in cases where a subject experiences an increase in symptoms consistent with a COPD exacerbation. Participants will be seen within 7 days of symptom onset.

Study burden and risks

Burden and risk associated with participation:
Nasal swab collections have the potential to irritate the intranasal cavity and lead to acute epistaxis; however, the risks associated with discomforts from such events are minimal. Additional risks include obtaining blood that may sometimes cause pain at the site where the blood is drawn, bruising, performing spirometry may cause mild chest tightening and coughing. There are no other risks to subjects in this study above that from the usual treatment of their disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria:
- Age *40 years at recruitment.
- Smoking history of *10 pack years.
- COPD patients with an FEV1/FVC <0.7.

Exclusion criteria

Exclusion criteria:
- Patients with a history of asthma, significant bronchiectasis, carcinoma of the bronchus, or other significant respiratory disease.
- Patients taking immunosuppressive medications.
- Active cancer diagnosis.
- Long-term steroid therapy (*10 mg/day).
- Females of childbearing potential without an efficient contraception.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-07-2017
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	07-04-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL60190.042.16
Other	volgt