The TARGET-ABC Study protocol
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A randomized, multi-center trial investigating if targeted antibiotic therapy can improve the prognosis in COPD patients infected with Pseudomonas aeruginosa.

Introduction:

COPD is a substantial global public health burden. In Denmark, about 14 % of the population over 35 years is affected by the disease (1,2). The course of COPD is complicated by recurrent acute exacerbations (AECOPD), which are characterized by increased dyspnoea, cough and mucus production. These events impair health status, accelerate the decline of lung function, worsen the prognosis and impose a significant economic burden on society (3).

Most exacerbations of COPD are caused by viral or bacterial infections. Pseudomonas aeruginosa (PA) are found in the airways in 5-20 % of the bacterial exacerbations, and is more likely to be isolated from patients more advanced disease and severe impaired lung function (4-9). The presence of PA in sputum samples is associated with prolonged hospitalization, increased exacerbation rate and poor long-term prognosis with mortality rates of 30 and 50 % after 1 respectively 3 years (10-12). However, it is difficult to draw definitive conclusions regarding the extent to which PA contributes to adverse clinical outcomes since reduced lung function (FEV1) in COPD also is a strong predictor of mortality. Infection with PA might therefore be secondary to damaged lung tissue and decreased lung function, and thereby have no independent impact on the prognosis. Infection with PA plays an important role in the course of other chronic lung diseases, in particular bronchiectases and cystic fibrosis (CF). Most patients with CF acquire a chronic PA infection, which is associated high morbidity and mortality (13). The importance of PA in COPD patients is less clear and the dynamics of carriage, host response and role of PA in the clinical course of COPD is less well characterized (14,15a+b). As of this, considerable uncertainty exists regarding the need for and approach to antibiotic treatment of PA infections. So far, no randomized controlled trial has been conducted to investigate whether specific antibiotic treatment of PA can reduce the risk of new exacerbations and improve the long-term prognosis of COPD patients.

Classical antibiotic therapies for PA in CF patients include piperacillin/tazobactam, meropenem, ceftazidime, aztreonam, gentamicin, tobramycin, colistimethate sodium and ciprofloxacin (16-21). Medications are primarily administered as combination treatment intravenously, as inhalation or as tablet. In Denmark, the first choice of treatment for PA infection is usually a 10-14 day therapy of

intravenous combination treatment of PA active antibiotics (piperacillin/tazobactam and ciprofloxacin) (22). Guidelines for treatment of PA infection in COPD are based on experience and minimal evidence.

Thus, PA represents a potentially significant cause of AECOPD and is associated with significant morbidity and mortality. The role of PA in the course of COPD is however less well characterized, and to date, evidence based guidelines for management and treatment of PA infection are lacking. With this study, we wish to increase the understanding of the clinical significance and consequences of PA infection in COPD patients.

Aim of the study:

To investigate whether antibiotic intervention with targeted, pseudomonas active agents in COPD patients with PA can reduce the loss of lung function, reduce the frequency of exacerbations and mortality.

Methods:

Trial and intervention:

Prospectively, randomized, 'open label' study of 150 ambulatory COPD patients with PA positive sputum samples. Patients are allocated and evenly distributed to the following treatment arms:

1. Control group: Oral tablet Ciprofloxacin 500 mg twice daily for 14 days.
2. Intervention: Intravenous Piperacillin/tazobactam 4 g three times daily + oral tablet Ciprofloxacin 500 mg twice daily for 14 days.

Inclusion criteria:

- 1 positive sputum sample for PA
- COPD (verified by pulmonologist based on clinical and spirometric criteria)
- Minimum 1 previous AECOPD requiring hospitalization/ emergency department visit and administration of systemic prednisolone +/- antibiotic treatment within the last 12 months
- Completed and signed informed consent

Exclusion criteria:

- Immune-modulating therapy (except ≤ 5 mg prednisolone/day) □
- Men < 40 years
- Women <55 years
- Non- menopausal women > 55 years *
- Life expectancy < 90 days
- Severe mental illness
- Severe language difficulties or inability to provide informed consent
- Known drug allergy to fluoroquinolone
- GFR <30 ml / min

  * Definition: has had menstruation within the last 12 months

Primary end-point:

- Time to systemic corticosteroid and/or antibiotic requiring AECOPD (in both primary and secondary sector).

Secondary end-points:

- Death within 12 months
- Frequency of re-admissions with AECOPD within 12 months.
- Frequency of non-invasive ventilation (NIV) or respiratory therapy during hospitalization
- Change in FEV1 from baseline
- Fall in FEV1 from baseline ≥ 200 ml /year
- Change in COPD Assessment Test (CAT) from baseline
- Changes in body mass index (BMI) from baseline
- Re-infection with Pseudomonas aeruginosa (new positive sputum culture)

Sample size estimation and calculation:

Sample size is calculated based on the following conditions and estimates:

1. Type 1 error = 5%. Power 80%
2. PA incidence = 5-20%
2. 67% of patients in the control group has had an AECOPD or have died within 12 months.
3. 47% of patients in the intervention group has had an AECOPD or have died within 12 months.

We expect an effect size of 20% absolute reduction (30% relative reduction) of mortality and exacerbation in the intervention group. To avoid estimate errors and risk of including too few patients (under-powering), the study is being "event driven" and will close when 67% of the patients in the control group has achieved an event (exacerbation or death).

Research plan and data acquisition:

The primary daily project management is handled by the project manager (PhD student Josefin Eklöf). A trained group of investigators, consisting of healthcare professionals from the departments involved, will assist the project manager with recruitment, sampling and follow-up of the patients. Data will be collected in case report forms (CRF), specific to each patient. Blood samples are taken at the entrance of the studio, and before administration of antibiotics, and will be monitored every third day via laboratory technician or project nurse/PhD student. Furthermore, a GCP unit will regularly monitor the trial.

In order to identify any underlying dissemination of emphysema and bronchiectases, a HRCT will be performed in each patient at study entrance. Moreover, a research bio bank will be created containing:

1. Whole blood from the time of enrollment.
2. The EDTA plasma and citrate plasma from inclusion time as well as after 7 and 14 days.
3. Pseudomonas Aeruginosa isolates of clonal/genetic analysis (see ‘on-going pathophysiological trials’ for further information).

Follow-up:

Ambulatory visits are planned at 14, 30, 60, 90 and 360 days after study entry.

Following procedures will be performed:

- Spirometry
- Sputum sampling
- Registration of medical adherence and possible drug adverse events/reactions
- Final follow-up of both primary and secondary end-points after 12 months

Side effects and health risks:

The treating physician can at any time chose to discontinue the antibiotic treatment if it is considered contraindicated. All medical adverse events and adverse effects, including possible severe cases, will be reported to the Danish Medical Agency. No severe side effects are expected during blood sampling. Performance of HRCT will expose the study participants to radiation equivalent to about 5 years of background radiation in Denmark. Since the median life expectancy for this group of patients with severely impaired pulmonary function is only about 5 years, and due to the fact that the radiological examination is planned as a single intervention, the diagnostic benefits to the patients are considered to outweigh the risk of exposure to radiation.

Ethical considerations:

The study has obtained the necessary approvals from the Research Ethics Committee (H-15010949) and the Danish Medicines Agency.

The study method has been carefully considered in order to be able to apply relevant and safe research results to clinical practice. The trial will conclude whether targeted antibiotics may benefit future COPD patients in terms of increased quality of life, reduced morbidity and mortality, and thus also benefit society by reducing the total economic cost of this large group of chronically and severely ill patients. It is our conviction that the trial is ethically responsible and can be implemented without exposing trial participant for unwanted and unnecessary risks. The patients may at any time withdraw their participation consent and exit the research project without affecting their right to present or future treatment.

Publication of results:

The project is part of a Ph.D. thesis. The test results will be published in peer reviewed journals regardless of whether they are positive, negative or in-conclusive.

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