

Helicoppter-study

The *Health in COPD by Personalized-eosinophil-guided IL-5-block-mediated corticosteorid sparing study*

Responsible for study:

Jens-Ulrik Stæhr Jensen

Research Associate Professor, Head, Respiratory Medicine Section (HGH University Hospital)

In association with Jørgen Vestbo, Professor of Respiratory Medicine, The University of Manchester

Steering Comittee:

COP:TRIN

se: <http://coptrin.dk/steering-committee-members/>

Scientific Project Sponsor:

Chronic Obstructive Pulmonary Disease Trial Network: COP:TRIN – A network of independent COPD researchers in Denmark: www.coptrin.dk

Participating centers:

1. Department of Internal Medicine, Respiratory Unit, Gentofte University Hospital, Denmark
2. Department of Internal Medicine, Respiratory Unit, Herlev University Hospital, Denmark
3. Department of Respiratory Medicine, Hvidovre University Hospital, Denmark
4. Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen, Denmark
5. Department of Respiratory Medicine and Infectious Medicine, North Zealand University Hospital, Hilleroed, Danmark
6. Department of Respiratory Medicine, Amager University Hospital, Denmark

HELICOPPTER-study

Content

1	Background.....	2
2	Study Aim.....	3
2.1	Hypotheses	4
3	Study Design.....	4
4	Recruitment.....	4
4.1	Inclusion Criteria.....	5
4.2	Exclusion Criteria.....	5
5	Randomization, Blinding and Intervention.....	6
5.1	Randomization and Blinding.....	6
5.2	Interventions.....	6
6	Endpoints and Definitions	6
7	Research Plan and Data Acquisition.....	7
7.1	Flowchart.....	8
8	Sample Size for Trial and Observational Stadium 2	10
9	Storage of biological material.....	10
9.1	Biological material for future research.....	10
10	Side Effects and Risks	11
10.1	Adverse Reactions and Events.....	12
11	Economy.....	12
12	Authorship	13
13	Publication of test results.....	13
14	Health Research Ethics	13
15	Informed Consent	14
16	Information Regarding Damage Compensation	14
17	References.....	15

HELICOPPTER-study

1 Background

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major cause of hospitalization and is associated with increased risk of mortality. AECOPD contributes to long-term decline in lung function and physical activity, impairs quality of life and causes high socioeconomic costs (1).

Oral corticosteroids have been used for decades in the treatment of AECOPD, however the effect size on objective endpoints is disputed and the incidence of side effects, also severe side effects, is high. A recent Cochrane review has shown that systemic corticosteroids to AECOPD patients compared to placebo reduce the risk of treatment failure (defined as a need to intensify therapy, emergency department visits or hospital admission) with an NNT = 9 [7, 14])(2). Lung function measured up to 72 hours after treatment showed significant improvement of forced expiratory volume in 1 s (FEV₁) in the corticosteroid group (140 mL [90; 200]). However, the improvement could not be observed later in the disease course. Moreover, mortality was unaltered (OR 1.0 [0.60; 1.66]). However, the risk of steroid-induced side effects was more than doubled (OR 2.33 [1.59; 3.43]) in the corticosteroid group compared with the control group; NNH = 6 [4, 10]. At the same time, the proportion of side effects in the corticosteroid group (48.1%) was significantly higher than the control group (28.2%). The risk of hyperglycemia was substantially increased (OR 2.79 [1.86; 4.19]) and the absolute risk was 28.2%.

Long-term use of corticosteroids may cause serious infections, cataracts, hypertension, peptic ulcers, myopathy, adrenal insufficiency, diabetes, osteoporosis and increased risk of bone fracture (3,4). Furthermore, the peripheral blood eosinophil count appears to be a promising biomarker to direct corticosteroid therapy during COPD exacerbations (5,6). It has been shown that it is a predictor of re-exacerbations, length of hospital stay(7) and mortality in severe exacerbations(8) In patients with documented eosinophilic inflammation and frequent AECOPDs, interleukin-5 (IL-5) receptor antibody may be a potential target for intervention to block this cascade(9), since IL-5 is a potent regulator of eosinophil inflammation.

Previous studies have investigated COPD patients with unspecified eosinophilic phenotypes. A recent study, with patients with a history of severe AECOPD who was then treated with anti-IL5 at a dose of 100 mg every 4 weeks which was in general negative but a subgroup analysis showed a positive effect in patients with a blood eosinophil count $\geq 0,3 \times 10^9/L$ (10).

HELICOPPTER-study

Another study of COPD patients with sputum eosinophilia randomized to IL-5 receptor blockade was in general negative, however, subgroup analysis revealed a possible effect in patients with blood eosinophil count of $\geq 0.4 \times 10^9/L$ supporting further investigation of the drug in patients with COPD and eosinophilia(11)

AECOPD causes worsening in COPD-patients health status, physical activity, lung function and leads to hospitalization and mortality. Until now exacerbations are treated with moderate to high doses oral corticosteroids, but that often leads to many side effects for instance hyperglycemia, sepsis, fractures(12) and venous thromboembolism. In addition, corticosteroids may be less efficacious in treating acute COPD exacerbations in patients with lower blood eosinophil levels (5), which is why this trial seeks to investigate whether IL-5-receptor-blocker- medicaments, which has already been tested to treat eosinophilia in severe asthma(13), can be a promising alternative to corticosteroids.

2 Study Aim

The aim of this trial is, in a population of patients with eosinophilic count $\geq 0.4 \times 10^9/L$ (within last 12 months) and ≥ 2 AECOPD within 12 months, to determine whether Reslizumab (IL-5 receptor blocker) can

- i) reduce the annual exacerbation rate compared to placebo
- ii) reduce the annual accumulated use of systemic corticosteroids compared to placebo
- iii) decrease glucose intolerance (HbA1c-detected), bone mineral loss (biomarkers-detected), or adrenal insufficiency (measured by peak cortisol levels in Synacten®test) compared to placebo.

HELICOPPTER-study

2.1 Hypotheses

Among COPD “frequent exacerbators” (≥ 2 exacerbations within last 12 months) who are genetically susceptible to corticosteroid-induced side effects* and who have had blood eosinophils $\geq 0.4 \times 10^9/L$ within the last year,

- administration of Reslizumab, can reduce the annual exacerbation rate compared to placebo.
- administration of Reslizumab, can reduce the annual accumulated dose of systemic corticosteroids compared to placebo.
- administration of Reslizumab can reduce the relative glucose intolerance (measured by HbA1c difference), bone mineral loss (measured by bone mineral biomarkers) and adrenal insufficiency (measured by peak cortisol in synacthen-test) compared to placebo.

3 Study Design

The study will be conducted as a prospective, randomized, multicenter, double-blinded, placebo-controlled study in patients with moderate/severe COPD.

The trial will include 146 patients in total from six respiratory departments in Denmark and England. The trial will have a screening/running period of 3 months.

4 Recruitment

In each center will the respective research leader be responsible for consecutive screening of new patients for inclusion. Patients admitted in a pulmonary department with AECOPD will be considered for inclusion based on the inclusion- and exclusion criteria. If a patient is suitable for the study, they will be invited to an ~~inclusion~~-screening meeting. A Good Clinical Practice (GCP)-trained nurse or Phd-student will be responsible for this step. If the patient fulfill the inclusions criteria, then they can be included.

The screening meeting will take place in an undisturbed office, meeting room or ambulatory and the patients will in advance be informed about their rights to bring a companion to the meeting. After the screening meeting, where the patient receives information about the informed consent necessary for participating in the study, the patients will be given 2 weeks for consideration to participate in the study. If the patient gives consent for participating within the 2 weeks after the screening meeting, then the randomization can take place and the placebo or intervention can begin.

HELICOPPTER-study

The primary investigator will be responsible for this step with the help from af GCP-trained nurse. The nurse will not be responsible for the randomization.

Within the 2 weeks the patient must also consider whether they will give their informed consent to storage extra blood and sputum sample for future research. They will be informed about this at the screening meeting. This is not mandatory for participating in the study.

Following information from patient's record will be given directly to the investigator from the responsible health care professionals at recruitment at the specific study site; age, gender, current and past diseases and, hospital admissions, results from paraclinical analyses and current and previous prescribed medications.

Following patient record information will be collected after study inclusion; contacts with the health care system including hospital admissions, results from paraclinical examinations and prescribed medications.

4.1 Inclusion Criteria

- ≥ 2 moderate AECOPD (treated with systemic glucocorticoids and/or antibiotic agents within last 12 months **or**
 ≥ 1 severe AECOPD (requiring hospitalization) with last 12 months
- Age ≥ 40 years
- Spirometry- and specialist verified COPD (defined as $FEV_1 / FVC \leq 70\%$)
- A FEV_1 after bronchodilator use $>20\%$ and $\leq 80\%$ of the predicted value
- Blood eosinophil count of $\geq 0.4 \times 10^9/L$ within the last 12 months

4.2 Exclusion Criteria

- Known asthma diagnosis
- Life expectancy less than 30 days
- Known allergy to systemic corticosteroids or Reslizumab
- Severe mental illness which is not controlled by medication
- People who are detained under the act on the use of coercion in psychiatry
- Severe language difficulties or inability to provide written informed consent

HELICOPPTER-study

5 Randomization, Blinding and Intervention

5.1 Randomization and Blinding

Randomization to standard treatment or Reslizumab will take place via a Web-based system. The randomization service provides a facility for emergency unblinding of treatment allocation which can be accessed by the a GCP-trained primary investigator at the specific study site.

Randomization will be in blocks of differing size and patients will be pre-stratified for age (segregation at 70 years), site of recruitment and FEV₁% (segregation at 50%) and eosinophil-concentration (segregation at $0,5 \times 10^9/L$) to ensure a balanced allocation across the two treatment groups.

Blinding will be performed by introducing placebo Reslizumab in the control group. Corticosteroids will not be blinded since they are merely a part of the standard-treatment in both arms: however, the risk of information-bias is eliminated since the Reslizumab intervention is double-blinded.

5.2 Interventions

In the *intervention arm*, Reslizumab will be administered according to the following dosing regimen: 3mg/kg mg intravenous injection every 4 weeks for 12 months.

All other aspects of therapy will be left to the discretion of the treating physician, including the use of inhaled drugs. Any monotherapy, dual therapy or triple therapy of the following drug groups can be used: Inhaled corticosteroids (ICS), Long Acting Beta-Agonist (LABA), Long Acting Muscarinic receptor Antagonists (LAMA) as well as short acting bronchodilators (SABA).

The *control arm* will receive placebo. All other aspects of therapy will be left to the discretion of the treating physician, including the use of inhaled drugs. Any monotherapy, dual therapy or triple therapy of the following drug groups can be used: ICS, LABA, LAMA as well as short acting bronchodilators.

6 Endpoints and Definitions

The primary endpoints of this study:

- To assess the “AECOPD burden” which is measured in the following ways:
 - Number of AECOPD* or death within 12 months (Incidence rate)
 - Time to next AECOPD* or death within 12 months

HELICOPPTER-study

The secondary endpoints of this study are:

- Accumulated dose of systemic corticosteroids per patient within 12 months (median, interquartile range)
- Composite endpoint of corticosteroid side effects consisting of: Glucose intolerance (defined by HbA1c), bone mineral loss (defined by bone mineral biomarkers) and adrenal insufficiency (measured by peak cortisol levels in Synacthen®-test) 6 months after baseline.
- Hospitalizations within 12 months
- Radiologically documented pneumonia within 12 months
- Treatment failure: Reexacerbation of COPD resulting in emergency department visits, hospitalization or need to intensify pharmacological treatment within 30 days
- Change in lung function (Δ FEV₁), Medical Research Council (MRC) scale and body mass index (BMI), COPD Assessment Test (CAT[®]) at 30 days and 12 months
- Infections requiring antibiotics within 180 days after the index AECOPD

*defined as moderate or severe based on the 2019 Global Initiative for Chronic Obstructive Lung Disease strategy paper: “COPD exacerbations are defined as an acute worsening in respiratory symptoms that result in additional therapy. These events are classified as mild (treated with short acting bronchodilators (SABDs) only), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or severe (patient requires hospitalization or visits the emergency room).

7 Research Plan and Data Acquisition

After inclusion patients will be randomly assigned 1:1 ratio to receive either intravenous injection (3 mg/kg Reslizumab) every 4 weeks or placebo.

Reslizumab should be administered every 4 weeks for 52 weeks, where the final dose is given in week 48. Final follow up on primary and secondary endpoints after week 52. The trial ends 12 months after inclusion of the last patient, then the analysis phase begins. The analysis phase is expected to last for 5 years.

HELICOPPTER-study

7.1 Flowchart

	Screening period	Baseline	Observational Period							
						Every 4 weeks		Every 4 weeks		Follow up
Visit	1	2	3	4	5	6-8	9	10-14	15	16
Weeks		0 (day 1)	4	8	12	16-24	28	32-48	52	52<
Initiation procedures										
Informed consent	X									
Confirm in-/exclusion criteria	X									
Standard blood sample	X									
For biobank to future research*										
Sputum sample	X				X				X	
Blood sample	X				X				X	
Administration of Reslizumab		X	X	X	X	X	X	X	X	
Efficacy										
BMI		X	X							X
MRC		X	X							X
CAT		X	X	X	X	X	X	X	X	X
Spirometry (FEV₁)		X	X	X	X	X	X	X	X	X
Synacthen®-test (Cortisol and ACTH)		X					X			
Bone mineral biomarkers (CTX and P1NP)		X					X			
Glucose intolerance test		X					X			

HELICOPPTER-study

Tests for biobank to future search* is not mandatory to participate in this study, but the samples will be available for future research if projects have separate approval from Research Ethics Committee. These sputum and blood samples will only be collected if the patient sign a separate informed consent.

The inclusion of patients, data collection, processing, statistical analysis, and publishing the data will be performed by medical doctor (coordinating investigator), Ph.d. student Anna Kristensen in cooperation with primary- and subinvestigators at the participating study sites, supervisors and members of the steering committee. Therefore, there is a high possibility that the project will be implemented. The project is expected to start with inclusion of patients from 1st of September 2019 and the last patient is expected to be included by end of September 2022. Data collection ends in September 2023. The Ph.d. student will be responsible for completing blood sampling, questionnaires and the different examinations in scheduled time. Decisions of medical issues are done by a doctor only.

The coordinating investigator (Ph.d. student) is responsible for proper handling (including storage) and delivery of the medication in cooperation with the investigators of the 6 centers. The investigator at each center keeps accounts of medicine (reception, delivery, return and destruction documented).

Also, an agreement with GCP unit at the University of Copenhagen will be signed in order to monitor the trial of the 6 centers.

Collected data will be treated confidentially by the staff assigned to the project. All data will be handled according to the Danish law for Privacy Regulation (Persondataforordningen) and the law for Data Protection (Databeskyttelsesloven). Data will be reported in electronic case report forms (e-CRF) specifically for each patient. The data includes demographic data, health status, current illnesses and other medical treatment, side effects, clinical and paraclinical test results and whether the various examinations are conducted. E-CRF is kept in the archives of the departments involved for 15 years. Data in e-CRF is entered by the investigator at each center.

- 1.** Medication will be recorded in a medication form as a part of the eCRF. The medication will be transferred from the electronic medical system used to administer medicines, in Denmark "Fælles MedicinKort, FMK". If patients are admitted to the hospital, the hospital medicine form will be used to feed the eCRF. Adherence will be discussed at all study visits and the eCRF medication form will be adjusted according to this.

HELICOPPTER-study

8 Sample Size for Trial and Observational Stadium 2

The sample size is based on an expectance of 25% less AECOPD within 12 months. This expectancy is based on the subgroup analysis from trial data (10). It is expected that 80% of standard care patients have at least 2 AECOPD within 12 months and less than 60% of patients in the intervention group experience at least 2 AECOPD within 12 months (RR 0.75). α is set at 0.05 and β is set at 0.2 (= Power 0.8). Based on these set values and estimates, a total of 146 patients are needed (82+82). The analysis of the secondary endpoints all demands fewer patients.

After analysis of the primary and secondary endpoints in the primary publication, inclusion will be continued in an observational study setting until 1200 patients have been recruited to build up a cohort of well-described COPD patients with frequent exacerbations and eosinophile phenotype. In this stadium 2 of the study, no interventions will be performed. In this stadium 2 of the study, no interventions will be performed. The Stadium 2 will be done to allow for biobank studies.

Number of sites and feasibility

Six (6) sites will participate in Denmark and UK, corresponding to approx. 25-30 patients recruited per site for the trial. It is estimated upon international data that approx. 10-15% of outpatient COPD GOLD C/D patients fullfill this. At each of the participating centers, 1000-2000 COPD GOLD C/D patients are treated, and thus approx. 100-300 patients are candidates for the trial at each site and totally, the number of possible candidates within the six participating centers will be 600-1800.

9 Storage of biological material

Biological material for this trial

Blood samples for the gene test, bone mineral biomarkers and Synacthen®-test, in total 200 mL, will be stored in a biobank freezer at -80 °C. The samples will be assessed during the projects analytic phase. The biobank will expire the 1th of September 2035, if there remain any blood samples they will be transferred to the biobank for future research.

9.1 Biological material for future research

There will be created a biobank to future research with the intention to benefit COPD research in the future. The biomarkers collected during the trial will be stored for later unspecified analysis. The samples will be locked away and stored pseudo anonymized for 15 years (until the 1th of September 2035) according to present legislation. The biobank will only be available to other trials if

HELICOPPTER-study

they have a separate approval from the Research Ethics Committee. The participating patients will also need to sign a separate informed consent to allow their material being stored.

Plasma and serum banking

There will be collected plasma and serum for biobanking. In total 100 mL during 365 days will be stored at -80 °C for later unspecified analysis.

Sputum banking

3 x 3 sputum samples will be stored at -80 °C for later unspecified analysis.

10 Side Effects and Risks

Reslizumab is a drug is tested and developed to treat severe eosinophilic asthma, which is why some side effects are already known.

According to pro.medicin.dk is the side effects of Reslizumab treatment are:

Very common (>10%): Headache

Common (1-10%): Reactions at the injection site, temperature rise, abdominal pain, nasal clogging, pharyngitis, back pain, eczema, allergic reactions such as angioedema, urticaria and bronchospasm, infection in lower respiratory tract and urinary tract infection.

Rare (0,01-1%): Anaphylactic reaction.

During the trial blood samples will be taken from patients to monitor their blood eosinophil concentration. Most often performing a venipuncture will not cause any complications. Though most typically (5-15%) patients can experience redness around puncture site caused by small bleeding in and under the skin.

Side effect to the Synacthen® test is very rare. Dizziness, rash, shortness of breath, nausea and vomiting have been reported.

HELICOPPTER-study

10.1 Adverse Reactions and Events

An Adverse Reaction (AR) is defined as any hurtful and unwanted reaction to any experimental drug regardless of the dose. The study is interested in evaluating the long-term effects, and will only register side effects, that are not already listed above.

An Adverse Event (AE) is defined as any unwanted event to a patient in a clinical trial after treatment with a drug, regardless of the connection between the treatment and the adverse event. Following events are natural and expected in this type of patients (COPD): cough, dyspnea, mucous in the airways, chest pressure, stridor, anxiety, swelling of lower legs, disturbance of sleep, general unrest, loss of appetite, tiredness and dizziness. Which is why these will not be reported.

A Severe Adverse Event/Reaction (SAE) is defined as an adverse event or adverse reaction, which will result in the death of a patient, is life-threatening or leads to hospitalization or prolongs hospitalization. If a severe adverse reaction occurs, the coordinating investigator and sponsor should be informed by the primary investigator within 24 hours after the primary investigator was aware (exacerbation of COPD will not be registered as a severe adverse reaction, but as an outcome).

The product resume of Reslizumab will be used as reference to consider whether a SAE was unexpected and then defined as a Suspected Unexpected Serious Adverse Reaction (SUSAR). The coordinating investigator and sponsor is responsible for informing Danish Medicines Agency (SST) about any SUSAR no later than 7 days after being informed about an SAE by the primary investigator. The registration of AE, AR, SAE and SUSAR continues until last treatment infusion (planned at week 48). At the end of the trial, a complete list of all SUSARs, adverse reactions and adverse events will be produced and reported to SST.

11 Economy

COP:TRIN is the organization behind this study. In cooperation with the members of the steering committees and project partners COP:TRIN will apply for economical support at relevant funds. The aim is to finance aid to the investigators, salary for other helping personnel, laboratory equipment and investigations.

Research Associate Professor, Section Head (Respiratory Medicine), senior consultant, Jens-Ulrik Stæhr Jensen, PhD will be main applicant and principal investigator. Co-applicants will be site investigators from the participating sites and from the main collaborative units.

HELICOPPTER-study

Due to the high costs of the drug Reslizumab, this study can only be conducted, if a company which produces the drug chooses to donate the needed amount of Reslizumab to the project. This company (three producers) will have no other interference with the study; nor the study design, execution of the trial, data processing or analyses. The company will not be part of the steering committee of the trial.

Patients will not receive any economical compensation for participating.

Research Ethics Committee and all participating patients will be informed if the project obtains economical support.

12 Authorship

Authorship is awarded overall according to the amount of scientific and practical work. Project coordinator and initiator (s) are obligatory authors. The participating departments will have a proportion of authorships according to the number of patients delivered to the overall study. On each site, the site Principal Investigator (possibly, 2, if it is shared) will have the primary right to co-authorship. Investigators who have recruited 10 or more patients will have the right to authorship. The above is the overall framework for authorship. If a disagreement arises, this should be settled by the Steering Committee.

13 Publication of test results

The project is part of a Ph.D. thesis. The test results will be published regardless of whether they are positive, negative or inconclusive. Publication in international peer-reviewed scientific journals is planned accompanied by parallel publications in the Danish Medical Journal. This includes at least one publication in a scientific journal with a high impact factor (10+). The members of the research group have a large and substantial track record of publishing in high impact journals like *The Lancet*, *The New England Journal of Medicine*, *The Lancet Respiratory Medicine* and others.

14 Health Research Ethics

AECOPD will worsen patient's COPD symptoms and cause patients to experience more dyspnea, cough and sputum than usual along with declining lung function and quality of life. Furthermore, it is associated with an increased risk of morbidity and mortality.

HELICOPPTER-study

Patients with frequent AECOPD are usually treated with repeatedly high doses of systemic corticosteroids. Although the treatment improves clinical recovery and have temporary effect on lung function, this treatment is associated with serious long-lasting side effect in terms of osteoporosis, infections, diabetes and adrenal insufficiency.

We aim to find information regarding, how patients with COPD should be treated in the future in a personalized rather than generalized manner. The study will investigate how to decrease use of corticosteroids (plus side effects) and achieve a better and longer lasting treatment result. Therefore, it seems reasonable to put patients through this project when the benefits in the long run seem greater than the losses. The tested drug has been shown to have relatively few and reversible side effects.

There are about 20,000 acute hospitalizations with AECOPD annually in Denmark, and these exacerbations represent a large burden on healthcare. If the outcome of this study shows a reduction in the annual rate of re-exacerbation rate, this will, in addition to helping this patient group, have a high socio-economic benefit.

The trial will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and the applicable country-specific regulatory.

15 Informed Consent

The inclusion of patients depends on signed consent form before inclusion. Patients are at any time able to withdraw their consent and leave the study without affecting their future treatments.

16 Information Regarding Damage Compensation

Participating patient, who think they have suffered damage, can apply for compensation through danish patient compensation (<http://patienterstatningen.dk/> cf. danish law).

HELICOPPTER-study

17 References

1. Wang Q, Bourbeau J. Outcomes and health-related quality of life following hospitalization for an acute exacerbation of COPD. *Respirology*. 2005;10(3):334–40.
2. Irwin RS, Madison JM. Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *N Engl J Med* [Internet]. 2003;348(26):2679–81. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMe030034>
3. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Joseph Melton L, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res*. 2004;19(6):893–9.
4. McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM, et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(3 PART I):704–9.
5. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: A randomized placebo-controlled trial. *Am J Respir Crit Care Med*. 2012;186(1):48–55.
6. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, et al. Acute exacerbations of chronic obstructive pulmonary disease: Identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med*. 2011;184(6):662–71.
7. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JEA, Morgan MD, Brightling CE, et al. Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. *Chest* [Internet]. 2016 Aug 1 [cited 2018 Nov 7];150(2):320–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26851799>
8. Steer J, Gibson J, Bourke SC. The DECAF score: Predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2012;67(11):970–6.
9. Bafadhel M, McCormick M, Rugman P, Dodson P, Pavord ID, Newbold P, et al. Sputum IL-5 Concentration Is Associated with a Sputum Eosinophilia and Attenuated by Corticosteroid Therapy in COPD. *Respiration*. 2009;78(3):256–62.
10. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2017;NEJMoA1708208.
11. Dalton JA, Higgins MK, Miller AH, Keefe FJ, Khuri FR. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med*. 2014;38(5):457–64.
12. Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of

HELICOPPTER-study

oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. 2017;357:j1415.

13. Varricchi G, Bagnasco D, Ferrando M, Puggioni F, Passalacqua G, Canonica GW. Mepolizumab in the management of severe eosinophilic asthma in adults: Current evidence and practical experience. *Ther Adv Respir Dis*. 2017;11(1):40–5.