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Anti-IL5 therapies for chronic obstructive pulmonary disease (Protocol)

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[Intervention Protocol]

Anti-IL5 therapies for chronic obstructive pulmonary disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of monoclonal antibody therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) compared with placebo in the treatment of adults with COPD.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a common condition characterised by persistent respiratory symptoms and airflow limitation. Chronic exposure to noxious particles or gases, most commonly tobacco smoke, leads to inflammation and narrowing of the airways (bronchitis) and parenchymal destruction (emphysema) (GOLD 2019). The cardinal symptoms are breathlessness, reduced exercise tolerance, wheeze and cough. COPD differs from asthma, the other major chronic airway disease, because its symptoms and airflow obstruction are not fully reversible. Acute exacerbations of COPD, which involve increased airway inflammation and sputum production, lead to increased symptoms beyond usual day-to-day variability. They are a major cause of morbidity, mortality, hospital admissions, and reduced quality of life for people living with COPD.

The global prevalence of COPD was estimated to be 251 million cases in 2016, accounting for 3.17 million deaths (5% of all deaths globally) during the previous year. It is projected to become the third leading cause of death worldwide by 2030 (WHO 2019a; WHO 2019b). In the UK, 4.5% of the population aged over 40 have a diagnosis of COPD (BLF 2019).

Phenotypic variation is seen between COPD patients, with variation in the proportion of cell types and cytokine profiles in affected airways. In more advanced disease, neutrophils and B lymphocytes predominate (Hogg 2004). A proportion of cases have eosinophilic airway inflammation, with elevated eosinophil counts in sputum or blood samples (blood eosinophilia > 2% was found in 37% of one cohort) (Singh 2014). Phenotypic clusters have also been identified during acute exacerbations, with up to 40% showing an eosinophil-predominant Th2 inflammatory profile (Saha 2006).

This has led to investigation into whether biomarkers, such as eosinophil levels, are associated with disease severity, exacerbation rates, and response to specific treatments. Correlation has been observed between elevated blood eosinophil levels and higher severe COPD exacerbation rates (Couillard 2017). The addition of an inhaled corticosteroid (ICS) to long-acting beta^2 -agonist

(LABA) therapy was more effective in preventing exacerbations in those with eosinophilia (Pascoe 2015). Systemic steroid treatment appears to be more effective in exacerbations where there is sputum or blood eosinophilia (Bafadhel 2012; Bafadhel 2014). These data point towards eosinophils playing a role in the pathogenesis of COPD, particularly during exacerbations, in a subset of patients.

Description of the intervention

Corticosteroids suppress inflammation non-specifically and are effective in many patients with asthma or COPD; a notable proportion, however, are poorly responsive. Moreover, frequent or continuous systemic corticosteroid use carries the risk of added morbidity, such as adrenal suppression, hyperglycaemia, osteoporosis and skin thinning.

In the search for more targeted treatments, monoclonal antibody (MAb) technology has been employed, with anti-IL-5 a commonly used MAb. The appeal of this approach is that MAbs can offer high affinity and specificity for targets not amenable to small-molecule drugs. They have revolutionised the management of other conditions, particularly certain connective tissue diseases, inflammatory bowel disease and cancers (Adegbola 2018; Bittner 2018). In all cases biomarkers are needed which can predict therapeutic responses, for example eosinophils, which infiltrate the airways. MAbs can then be directed against immune pathways which may contribute to the presence of eosinophils, such as interleukin 5 (IL-5).

T helper type 2 (Th2) cells and eosinophils are implicated in both COPD and asthma. Mediators including interleukin 3 (IL-3), IL-5 and IL-13 are prominent in Th2-type inflammation, where they promote eosinophil maturation. IL-5 is particularly key for the differentiation, proliferation and activation of eosinophils. Th2 cells can also drive airway inflammation via an IgE and mast cell mechanism. Several biologic drugs targeting Th2-type inflammation have demonstrated efficacy as an adjunct to corticosteroids in the management of severe eosinophilic or atopic asthma, with acceptable side-effect profiles (Farne 2017; Normansell 2014). Consequently, a number of them have been approved for use in this context, namely omalizumab (anti-IgE), mepolizumab (anti-IL-5), reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor).

There may also be useful drug targets outside the Th2-eosinophil pathway, although to date these have not shown such efficacy in airway diseases (Durham 2016; Nixon 2017).

How the intervention might work

Eosinophilic inflammation has been implicated in a proportion of patients with COPD, most prominently during exacerbations (Singh 2014; Siva 2007; Vedel-Krogh 2016). This process has been effectively targeted in severe eosinophilic asthma. Therefore it is postulated that MAbs directed against similar targets in COPD patients with eosinophilic phenotypes may provide therapeutic benefit.

Why it is important to do this review

Whilst COPD is an irreversible disease, its management is directed at slowing or halting the decline in lung function, preventing and aborting exacerbations, and optimising quality of life. Monoclonal antibody therapies have proven a useful tool for asthma. A recent Cochrane Review supports the use of anti-IL-5 treatments as an adjunct to standard treatment in people with severe eosinophilic asthma, with treatments roughly halving asthma exacerbations (Farne 2017). Given the number of pathological similarities between asthma and COPD, it may be that they can benefit at least a subset of COPD patients too. Anti-IL-5 treatments have not been approved for use in COPD and they are not mentioned in guidelines, but as there is an emerging literature in this field it is important to establish whether they have a role to play or not (Tan 2018). COPD is such a common condition that any additional treatments have the potential to benefit a large number of patients. Exacerbations are a major determinant of both quality of life and healthcare usage. These drugs reduce exacerbations of asthma (Farne 2017). If they also reduced exacerbations of COPD in those with eosinophils that would be good for patients and healthcare systems.

OBJECTIVES

To assess the efficacy and safety of monoclonal antibody therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) compared with placebo in the treatment of adults with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported in full text, those published as an abstract only and unpublished data.

Types of participants

We will include adults ($\geq$ 40 years old) with a diagnosis of COPD as defined by GOLD 2019. We will record study authors' definitions of the severity of COPD. We will not exclude participants

with co-morbidities. We will, however, exclude participants with a substantial asthma component to their disease, either with a label of "asthma COPD overlap syndrome" (Pavord 2015), or excessive variation in lung function, defined by a variation of more than 12% and 200 mL in FEV_1, either between tests or with a bronchodilator (GINA 2019).

Types of interventions

We will include studies comparing anti-IL-5 therapy with placebo. Specifically we will consider anti-IL-5 therapies developed for use in other airway diseases such as those directed against various IL-5 targets. We will include studies that allowed participants to continue using their inhaled therapies including inhaled corticosteroids (ICS), long-acting $beta_2$-agonist (LABA), and long-acting muscarinic antagonist (LAMA) or combination inhalers, as long as these co-interventions are not part of the randomised treatment.

Types of outcome measures

Primary outcomes

1. All exacerbations
2. Hospitalisations due to COPD exacerbation
3. Serious adverse events
4. Quality of life (as measured on a validated scale, e.g. St George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Disease Questionnaire (CRDQ))

Secondary outcomes

1. Measures of pulmonary function such as FEV_1, and FVC
2. Exercise performance- six-minute walk test and other measures
3. Self-rated symptom score/symptoms of breathlessness such as:
   i) inhaled rescue medication used during the treatment period and concomitant medication usage, including antibiotics and steroids;
   ii) number of days (or nights) participant experienced symptoms;
   iii) COPD Assessment Test (CAT) Score; or
   iv) COPD Control Questionnare (CCQ) Score.
4. Adverse events/side effects
5. Mortality

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from searches of the following databases and trial registries.

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date
2. Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date
3. MEDLINE Ovid SP 1946 to date
4. Embase Ovid SP 1974 to date
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov)
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

The proposed search strategy for the Cochrane Airways Trials Register is listed in Appendix 1. This will be adapted for use in the other databases. The search strategy was developed by the Cochrane Airways Information Specialist in collaboration with the authors.

We will search all databases and trials registries from their inception to the present, and there will be no restriction on language or type of publication. Hand-searched conference abstracts and grey literature will be identified through the Cochrane Airways Trials Register and the CENTRAL database in the Cochrane Library.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' web sites for study information.

We will search on PubMed for errata or retractions from included studies published in full text, and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (RW and TD) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (IC and PB) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (RW, TD or SM). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We

will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (RW and TD) will extract the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (IC and PB) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (RW, TD or SM). One review author (TD) will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (RW) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (RW and TD) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (IC, PB or SM). We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If we combine data from rating scales in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If we combine two comparisons (e.g. drug A versus placebo and drug B versus placebo) in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA) we will use these as a preference in our meta-analyses. If both change-from-baseline scores and endpoint scores are available for continuous data, we will use change-from-baseline scores. If a study reports outcomes at multiple time points, we will preferentially use 12-month data but report other time points where appropriate.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes we will use participants, rather than events, as the unit of analysis (i.e. number of people admitted to hospital, rather than number of admissions per person). If, however, rate ratios are reported in a study, we will analyse them on this basis. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible and we think the missing data introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We will use a random-effects model, reported with 95% confidence intervals (CI) and perform a sensitivity analysis with a fixed-effect model. We will synthesise and report dichotomous and continuous data separately for each outcome, e.g. hospitalisation/no hospitalisation or duration of hospitalisation. We will also analyse odds ratios and report them separately. For a given outcome measure, we will combine effect estimates, such as differences at endpoint and change from baseline. When outcomes are measured using different scales, e.g. health-related quality of life, we will use standardised mean differences (SMD) in the analyses. We will use the baseline standard deviation (SD) for the SMD analyses.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: all exacerbations, hospitalisations due to COPD, serious adverse events, lung function (FEV_1) and quality of life. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Baseline serum eosinophil counts (> 0.3 vs $\leq 0.3 \times 10^9$ per litre of blood)
2. Baseline COPD severity using GOLD 2019 classification

We will use our primary outcomes in the subgroup analyses. We will use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the following from the primary outcome analyses.

1. A comparison of available case analysis to true ITT analyses, where the ITT analyses are imputed.
2. A comparison based on the risk of bias assessment where trials are judged to be at high risk of bias for any of the six domains.

We will compare the results from a fixed-effect model with the random-effects model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Database search strategy

Database: Cochrane Airways Register of Trials
Platform: Cochrane Register of Studies

#1	MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2	MeSH DESCRIPTOR Bronchitis, Chronic
#3	(obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4	COPD:MISC1
#5	(COPD OR AECOPD OR AECB):TI,AB,KW
#6	#1 OR #2 OR #3 OR #5 OR #4
#7	MESH DESCRIPTOR Antibodies, Monoclonal
#8	MESH DESCRIPTOR Antibodies, Monoclonal, Humanized
#9	mepolizumab
#10	SB24056 or SB-24056
#11	Bosatria or Nucala

(*Continued*)

#12	benralizumab*
#13	MEDI-563
#14	Reslizumab*
#15	Cinquil or Cinqair
#16	CEP-38072
#17	anti-interleukin 5
#18	anti-IL5
#19	anti-IL-5
#20	MESH DESCRIPTOR Interleukin-5 EXPLODE ALL
#21	MESH DESCRIPTOR Receptors, Interleukin-5 EXPLODE ALL
#22	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	#22 AND #6

CONTRIBUTIONS OF AUTHORS

TD: contributed to Methods, Data collection and Analysis sections

SM: contributed to Background and Methods sections

RW: contributed to Methods, Data collection and Analysis sections

IC: contributed to Methods section

PB: contributed to Background and Methods sections

Contributions of editorial team

Rebecca Fortescue (Coordinating Editor): edited the protocol; advised on methodology; approved the protocol prior to publication.
Chris Cates (Coordinating Editor) checked the planned methods.
Han Ni (Contact Editor): edited the protocol and advised on content.
Emma Dennett (Managing Editor): coordinated the editorial process; advised on content; edited the protocol.
Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the protocol.
Elizabeth Stovold (Information Specialist): designed the search strategy; arranged for peer review of the search strategy.

DECLARATIONS OF INTEREST

TD: none known

SM: none known

RW: none known

IC: I work in a clinically relevant speciality (respiratory medicine). I have been involved as a local investigator for a GSK-sponsored drug trial in COPD but not of the drugs under consideration in this review.

PB: I work in a clinically relevant speciality (respiratory medicine).

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Salary for TD

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