Study protocol

Study title

Phenotyping Asthma Exacerbations in primary care: an electronic medical record study (PHASE)

Protocol number

OX-2024-IH

Sponsor

University of Oxford

Author

Dr Imran Howell

Respiratory Medicine Unit, Nuffield Department of Medicine, John Radcliffe Hospital, OX3 9DU

Collaborator/co-author

Prof Ian Pavord

Respiratory Medicine Unit, Nuffield Department of Medicine, John Radcliffe Hospital, OX3 9DU

Collaborator/co-author

Prof David Price

Observational and Pragmatic Research Institute (OPRI)

Collaborator/co-author

Dr Simon Couillard

Faculté de médecine et des sciences de la santé, Université de Sherbrooke

Collaborator/co-author

William Henley

Observational and Pragmatic Research Institute (OPRI)

Collaborator/co-author

Heath Heatley

Observational and Pragmatic Research Institute (OPRI)

Responsible parties

1. Dr Imran Howell
   Primary investigator
   Clinical Research Fellow
   University of Oxford

Imran.howell@ndm.ox.ac.uk
Tel: 01865221538
Address: Respiratory Medicine Unit, Nuffield Department of Medicine, John Radcliffe Hospital, OX3 9DU

2. Prof Ian Pavord
Co-primary investigator
Professor of Respiratory Medicine
University of Oxford
Ian.pavord@ndm.ox.ac.uk
Tel: 01865221538
Address: Respiratory Medicine Unit, Nuffield Department of Medicine, John Radcliffe Hospital, OX3 9DU

3. Prof David Price
Co-primary investigator
Director of Observational and Pragmatic Research Institute (OPRI)
Professor of Primary Care Respiratory Medicine
University of Aberdeen
david@opri.sg
Address: University of Aberdeen, AB25 2ZD

Hypothesis

We hypothesise that there are blood eosinophil high and blood eosinophil low asthma exacerbations in primary care and that distinguishing these exacerbation phenotypes informs on aetiology, prognosis, and treatment outcomes.

Aims

The primary aim of the study is to investigate whether blood eosinophil count (BEC) measured at stable state and/or exacerbation can discriminate between different exacerbation phenotypes and different clinical responses to oral corticosteroid and/or antibiotic treatment at exacerbation in primary care.

The secondary aim of the study is to assess if low-BEC exacerbations predominate in winter, are more likely to be diagnostically labelled as infective by the clinician, and more frequently treated with oral antibiotics

Rationale

Asthma exacerbations are a common and important problem that cause a high symptom burden, decline in lung function, and affect a person's physical activity, work, personal life, and mental health[1]. Over 80% of attacks are treated in primary care[2]. Asthma exacerbation treatment is heterogeneous with either oral corticosteroids (OCS), antibiotics, or both[3]. Evidence for OCS is based on randomised controlled trials demonstrating a reduction in relapse and a modest increase in the rate of symptom

recovery[4]. However, their effect in mild-moderate attacks is probably overestimated because the trials of OCS were in the 1980s when only 20% of people were treated with inhaled corticosteroids (ICS)[5]. ICS are very effective at reducing asthma attacks and are now standard treatment in all asthma patients. Antibiotics are frequently used, even though fewer than 20% of exacerbations are associated with bacterial infection and there is no evidence of their efficacy[6].

Type-2 inflammation is often present in patients presenting with asthma exacerbations, reflected by raised blood eosinophils and FeNO. We see a future where asthma exacerbation treatment is biomarker directed. We know that OCS are most effective in people with high levels of type-2 inflammation, but their duration of effect may be limited[7,8]. Recently, we have found in two independent studies (submitted for publication) in biologic-naïve asthmatics and biologic-treated asthmatics that type-2 inflammatory asthma exacerbations are more clinically responsive to OCS than type-2 low events[9,10]. Furthermore, in an investigator-initiated trial conducted at Oxford, blood eosinophil-directed benralizumab treatment of eosinophilic asthma exacerbations provided longer lasting treatment response[11] than prednisolone alone.

In type-2 low events, viral and bacterial infections, or other unexplored mechanisms, may play a key role. OCS treatment is less likely to be effective in type-2 low events and may not have an acceptable risk/benefit balance. This is because OCS are fraught with side effects. 75% of UK asthma patients experience a temporary side effect, and just three courses of OCS nearly double the 10-year relative risk of heart disease, diabetes, and osteoporosis[12]. Further, our research has shown that patients and healthcare professionals are willing to trade-off substantial asthma exacerbation treatment benefit in exchange for avoiding these steroid risks (submitted for publication). Together, these observational and trial data show that type-2 inflammatory stratification of asthma attacks may yield important clinical information and inform treatment decisions. Due to the overt differences in clinical trajectories and treatment responses between the type-2 high and low phenotypes, we speculate that the inflammatory profile of asthma attacks managed by general practitioners is distinguishable in clinical databases.

Our novel, real world project will explore the relationship between blood eosinophils and treatment response to OCS, antibiotics, or both in exacerbations in primary care. We anticipate that this will provide supportive evidence for biomarker treatment of asthma exacerbations. For blood eosinophil-high asthma exacerbations, this will be important real-world incidence and treatment outcome data to put the ABRA trial into context. For blood eosinophil-low exacerbations, we will understand if there are higher rates of treatment failure, more concurrent antibiotic use, and different diagnostic labelling. This information will provide a rationale for research to understand type-2 low exacerbation mechanisms. Additionally, it would help set the scene for a future biomarker-directed, placebo-controlled, randomised trial to determine the efficacy of prednisolone in type-2 low exacerbations in a primary care setting.

Primary Objective

1. Compare the rates of treatment failure (defined below) at 28 days for asthma exacerbations treated in primary care with oral steroids, or antibiotics, or both between high (>=0.3 x 10^9/L) and low (<0.3 x 10^9/L) blood eosinophil count (BEC) groups at steady state.

Key secondary objective

1. Compare the rates of treatment failure at 28 days for asthma exacerbations treated in primary care with oral steroids, or antibiotics, or both continuously by BEC at steady state

Other secondary objectives

2. Compare the rates of treatment failure at 14 days for asthma exacerbations treated in primary care with oral steroids, or antibiotics, or both continuously by BEC at steady state
3. Compare the rates of treatment failure at 14 days for asthma exacerbations treated in primary care with oral steroids, or antibiotics, or both between high (>=0.3 x 10^9/L) and low (<0.3 x 10^9/L) blood eosinophil count (BEC) groups at steady state.
4. Compare the rates of treatment failure at 14 and 28 days for asthma exacerbations treated in primary care with oral steroids, or antibiotics, or both between high (>=0.3 x 10^9/L) and low (<0.3 x 10^9/L) BEC groups on day of exacerbation.
5. Compare the rates of treatment failure at 14 and 28 days for asthma exacerbations treated in primary care with oral steroids, or antibiotics, or both continuously by BEC on day of exacerbation.
6. Explore the association between time to treatment failure up to 90 days, the continuous BEC value, and other covariates.
7. Characterise asthma exacerbations by BEC on day of exacerbation and examine their relationship with the time of year.
8. Record diagnostic labels used for asthma exacerbations and compare the use of steroids and/or antibiotics, and the rates of treatment failure

Primary Outcomes

1. Treatment failure at 28 days after exacerbation date, defined as:
    i) Acute prescription of oral corticosteroids and/or oral antibiotics in conjunction with an asthma or LRTI related primary care consultation
    ii) Admission to hospital, or emergency department visit, or out of hours healthcare visit, with asthma or LRTI as primary or secondary diagnosis.
2. Highest BEC in the last 12 months.

Secondary Outcomes

1. Treatment failure at 14 days after exacerbation date
2. Treatment failure at 90 days after exacerbation date
3. BEC on day of exacerbation
4. Blood CRP level taken on exacerbation date (if available)

5. Date of exacerbation
6. Diagnostic label of exacerbation (asthma attack/exacerbation; or LRTI; or other/undocumented)
7. Diagnostic label of pre-existing airways disease (asthma; or asthma/COPD)

Baseline data (for modelling interactions):

1. Demographics: age; gender; smoking status; BMI (if available within 5 years of exacerbation date)
2. Primary care asthma review in 12 months prior to the exacerbation date
3. Cambridge multimorbidity score at time of exacerbation
4. Presence of following co-morbidities at time of exacerbation: COPD; GORD; Chronic rhinosinusitis; nasal polyps; eczema; allergic/non-allergic rhinitis
5. FEV1, FEV1/FVC ratio, and/or percent predicted PEF (most recent recorded to exacerbation date)
6. Documented reversibility or variability
7. Airways pharmacotherapy in year prior to exacerbation date - SABA; ICS; LABA; LAMA; ICS/LABA; LABA/LAMA; ICS/LABA/LAMA; leukotrine receptor antagonists; methylxanthines; acute courses of antibiotics (respiratory indication); acute courses of oral corticosteroids
8. Asthma disease severity - number of exacerbations, hospital attendances, and emergency department attendances in the previous year
9. Average daily dose of ICS in the 12 months prior to the exacerbation date
10. GINA step at time of the exacerbation

Inclusion Criteria

1. Patients aged 12 - 100 with physician diagnosed asthma, an asthma diagnostic SNOMED code in the asthma registry, and no asthma-resolved SNOMED code after the last asthma diagnosis code.
2. Evidence of active asthma (at least 2 ICS prescriptions in the last 12 months)
3. Treatment of an exacerbation with oral steroids and/or oral antibiotics between 2000 - January 2020
4. The exacerbation date is the date of any asthma exacerbation in primary care, coded as either:
    i) Asthma exacerbation, or asthma attack, or acute asthma, or asthma, with prescription for oral corticosteroids and/or oral antibiotics
    ii) Lower respiratory tract infection (LRTI) with a prescription of acute oral corticosteroids with or without oral antibiotics
    iii) Prescription for oral corticosteroids (with or without oral antibiotics) without evidence of an asthma review on the same day
5. No treatment with oral corticosteroids or antibiotics in the 4 weeks before exacerbation
6. BEC recorded in the 12 months prior to the exacerbation date
7. Continuous electronic medical record data for the 12 months prior to, and at least 12 weeks following, the exacerbation date

Exclusion Criteria

1. A diagnostic SNOMED code for any of the following chronic respiratory conditions recorded at any time: bronchiectasis, pulmonary sarcoidosis, hypersensitivity pneumonitis, malignancy of the lungs, interstitial lung disease, and cystic fibrosis. (Patients with concomitant diagnosis of COPD not excluded).
2. Ever treated with either mepolizumab, benralizumab, reslizumab, dupilumab, tezepelumab, or omalizumab
3. Continuous OCS use in the 6 months prior to exacerbation.

Data management

This is a collaborative project between researchers at the University of Oxford and the Observational & Pragmatic Research Institute (OPRI) and Optimum Patient Care (OPC) led by Prof David Price. We will use the Optimum Patient Care Research Database (OPCRD) to reach as large a dataset as possible. OPCRD comprises data extracted through the OPC Clinical Service Evaluation. OPCRD contains anonymized, research-quality data for approximately 24 million patients from over 1000 GP practices, representing over a third of the UK population. This ensures that the study will have good external validity. The OPCRD database is approved by the Health Research Authority for clinical research use (Research Ethics Committee reference: 15/EM/0150), is governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. As this research study is a non-interventional, observational research, using anonymous data which does not require separate Research Ethics Committee approval in addition to ADEPT approval.

This study was designed and will be implemented and reported in accordance with the criteria of the European Network Centres for Pharmaco-epidemiology and Pharmacovigilance (ENCePP) study and follows the ENCePP Code of Conduct (EMA 2014). All data extracted to be transferred from sites will enter the research database in the form of anonymised patient IDs. The data will be retrieved by OPC Data Analysts and utilised as an anonymised dataset to perform the analysis according to protocol. Analysis will be conducted by Dr Imran Howell at the University of Oxford following a Data Transfer Agreement between University of Oxford and OPC.

The study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices. OPC complies with ISO 27001, ISO 9001, the NCSC Cyber Essentials, and the NHS Data Security and Protection Toolkit (ref: 8HR85) assessment annually. This ensures OPCRD complies with the UK National Data Guardian's data security standards, the GDPR, and global framework of information security, quality assurance and management.

Sample Size Justification / Statistical

Statistical analysis will be performed by Dr Imran Howell in collaboration with statisticians in OPRI. For the primary outcome, Cox proportional hazards regression analysis will be used to adjust for confounders (age, sex, BMI, FEV1, GINA step, season of exacerbation, co-morbid COPD) to estimate the association between BEC and treatment failure. This will be modelled using the BEC categories listed above. We will also run a recurrent event Cox model and a discrete-time Cox model. Kaplan-Meier curves will be performed with high/low blood BEC as a categorical variable.

For the key secondary analysis of BEC as a continuous variable we will log-transform BEC for the analysis. The Cox models will be represented graphically using a restricted cubic spline association the adjusted treatment failure hazard ratio (outcome variable) and BEC. This analysis will allow exploration of non-linearity and choice of BEC threshold for a future trial.

In terms of sample size for the primary outcome using the Cox-proportional hazards model, we have based calculations on a study with a similar population conducted by OPRI[3]. Assuming 30% of asthma patients have blood eosinophils <0.3 x 10^9/L, a hazard ratio of 0.8 in the high BEC group (corresponding to a 20% relative reduction in risk of treatment failure in the high BEC group), alpha 0.05, beta 0.1 then 1005 treatment failure events are required to detect a significant difference. Assuming a baseline event rate (treatment failure/4 weeks) of 30%[13], censoring rate of 20% and a planned follow-up of 4 weeks, then approximately 43,300 asthma patients with an exacerbation are required.

This is achievable with the size of the data set available through OPCRD. There are 2.1 million patients with active asthma and no exclusion criteria. Using conservative estimates that 20% have a recorded exacerbation in the study timeframe, and 25% of those have a valid blood eosinophil count in the 12 months preceding the exacerbation, this would still leave approximately 105,000 patients who have had an exacerbation that meets inclusion criteria.

1. Martin MJ, Beasley R, Harrison TW. Towards a personalised treatment approach for asthma attacks. Thorax 2020;75:1119-29.
2. Shah SA, Quint JK, Nwaru BI, Sheikh A. Impact of COVID-19 national lockdown on asthma exacerbations: interrupted time-series analysis of English primary care data. Thorax 2021;76:860-6.
3. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med 2015;3:849-58.
4. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database of Systematic Reviews 2007.

5. Edmonds ML, Milan SJ, Brenner BE, Camargo Jr CA, Rowe BH. Inhaled steroids for acute asthma following emergency department discharge. Cochrane Database of Systematic Reviews 2012.
6. Normansell R, Sayer B, Waterson S, Dennett EJ, Del Forno M, Dunleavy A. Antibiotics for exacerbations of asthma. Cochrane Database of Systematic Reviews 2018;6:CD002741.
7. Sahid El-Radhi A, Hogg CL, Bungre JK, Bush A, Corrigan CJ. Effect of oral glucocorticoid treatment on serum inflammatory markers in acute asthma. Arch Dis Child 2000;83:158-62.
8. Moran AM, Ramakrishnan S, Borg CA, et al. Blood Eosinophil Depletion with Mepolizumab, Benralizumab, and Prednisolone in Eosinophilic Asthma. Am J Respir Crit Care Med 2020;202:1314-6.
9. Howell I, Mahdi M, Bafadhel M, et al. Recovery of Breakthrough Asthma Attacks Treated With Oral Steroids While on Monoclonal Antibody Therapy: Protocol for a Prospective Observational Study (BOOST). JMIR Res Protoc 2023;12:e46741.
10. Carlos Andrés C-P, Simon L, Martine D, et al. Phenotyping the Responses to Systemic Corticosteroids in the Management of Asthma Attacks (PRISMA): protocol for an observational and translational pilot study. BMJ Open Respiratory Research 2023;10:e001932.
11. Acute Exacerbations Treated With BenRAlizumab (The ABRA Study) (ABRA). (Accessed 01/11/2022,
12. Skov IR, Madsen H, Henriksen DP, Andersen JH, Pottegård A, Davidsen JR. Low-dose oral corticosteroids in asthma associates with increased morbidity and mortality. Eur Respir J 2022;60.
13. Hill J, Arrotta N, Villa-Roel C, Dennett L, Rowe BH. Factors associated with relapse in adult patients discharged from the emergency department following acute asthma: a systematic review. BMJ Open Respir Res 2017;4:e000169.