Study protocol

Targeting therapy in people with severe asthma

A retrospective cohort study describing commonly measured biomarkers (eosinophil count and IgE levels) in patients with severe asthma

Version Final

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NSHI Ltd

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Title	Targeting therapy in people with severe asthma
Subtitle	A retrospective cohort study describing commonly measured biomarkers (eosinophil count and IgE levels) in patients with severe asthma
Protocol version number	Final
Study aim	To categorise people with severe asthma according to their total IgE and eosinophil biomarker status
Locus of study	Glasgow, Scotland

Contents

1.0 Background

With the introduction of novel therapies for asthma, it will be useful to differentiate patient need by clinical status (severity) and biomarkers.

Patients with severe asthma may be eligible for these potentially life transforming treatments. Biological therapies demonstrate successful outcomes but are (and as new therapies become available, will be) restricted in use by both an assessment of need after optimised care and a biomarker profile consistent with product licenses. Two biomarkers of interest are currently available in routine cllinical practice. Blood eosinophil count is available as part of the Full Blood Count, one of the most commonly conducted blood tests. Assessment of total and specific IgE levels are routinely measured as part of the workup-up for people with moderate–severe asthma. The biological therapy omalizumab may be indicated in patients with severe asthma and an appropriate, raised, IgE. Anti Il-5s (and other therapies) may be indicated in patients with severe asthma and raised blood eosinophil counts.

As periostin estimation is not currently in routine use, this biomarker (and its possible guide to Il-13 drug therapy) is not considered in this project.

One traditional view is that eosinophil counts and IgE levels are associated. Recent anecdotal evidence proposes that the relationship may not be consistent and that a group of patients who are both eosinophil high and IgE low may exist, for example.

By defining the biomarker status of a cohort of people with severe asthma we can estimate the potential impact of precision medicine through appropriate biological therapies for these patients.

Potential sample size: IgE levels are infrequently measured. A preliminary search of the NHS Greater Glasgow and Clyde (NHSGGC) Safe Haven database (n=1.4 million) revealed that about 10,000 IgE levels were requested last year (Dr Moira Thomas, Consultant Immunologist, personal communication). Of these, 1850 were from patients aged 18 years or over who had a Read or ICD code for asthma (Marion Flood, Safe Haven Manager, personal communication).

Setting: Because these data are only accessible through NHSGGC Safe Haven, the data needs to be collected, collated and analysed within the Safe Haven setting. Professor Amanda Lee and colleagues from the University of Aberdeen have the appropriate Good Clinical Practice (GCP) and Safe Researcher traing and approval, and the necessary programming/statistical skill to perform the statistical analyses. NHSGGC Safe Haven staff will provide the raw data.

The protocol will be registered with relevant databases.

Strengths of using a NHS region database approach:

- Whole service, non-selective population (compared to databases that practices voluntarily contribute to)

- Comprehensive, multi-source data collection (both primary and secondary care) regardless of patient locus ensures comprehensive reporting of outcomes

Limitations of using a NHS region database approach:

- Potential gaps in data due to incomplete coding in a service (rather than research) setting. This is a problem common to all clinical database work

2.0 Study aim and objective

2.1 Study aim

To categorise people with severe asthma according to their eosinophil and total IgE biomarker status.

2.2 Study objective

To produce the tables and figures as listed in section 5.4.

3.0 Data source

3.1 NHSGGC Safe Haven

NHSGGC Safe Haven forms part of the Scotland branch of **The Farr Institute**, which is a UK-wide network of federated Safe Havens. It is the result of a unique collaboration between NHS Greater Glasgow & Clyde Research & Development and the Robertson Centre for Biostatistics, offering an excellent resource for health-related data research in Scotland. All staff are trained in International Conference on Harmonisation (ICH) GCP and regularly undertake training in a variety of research related subjects. The goal is ambitious to achieve but simple in concept; to establish a large research resource which is able to link health information datasets at patient level, so as to provide answers to clinical research questions and inform health service improvement. It is committed to helping get the best possible outcome for research projects with the goal of improving the science behind the health service and, in so doing, improve the health service and provide increased patient benefit. The need for large datasets which provide valuable information for quantitative analysis, and which support qualitative research, has grown stronger over recent years and will become even more important in the future.

The demand for 'big data' to inform future healthcare; whether it be service improvement, new surgical techniques with lower post-procedural infection rates, more highly targeted drugs with less side effects, 'personalised' medicine using molecular genetics or highly sophisticated new nano-techniques, is enormous. This

also increases the potential investigative avenues for researchers to develop and utilise. The Safe Haven brings traditional research strategies and modern technology together to advance these avenues by providing a large health data resource managed by the NHS and supported by universities, in order toexploit the knowledge from both NHS and academic sources to future-proof our public health service.
Patient identifiable data is not released to researchers, but instead datasets are linked in-house before releasing the full research dataset in an anonymised format, safeguarding the public from the risk of identification. Research applications are also assessed for disclosure risk. Patient confidentiality and security is of utmost importance to NHS Scotland and the Safe Haven strives to ensure this is maintained, in accordance with statutory regulations, in order to maintain public trust – which is paramount.

4.0 Study design

This is a retrospective cohort, database study describing commonly measured biomarkers (IgE levels and eosinophil count) in patients identified with severe asthma.

4.1 Study period

Within the defined study population, analysis will focus on biomarker, prescription and medical data collected in the 2 years prior to the pre-defined index date 1st Jan 2016.

4.2 Study population

All patients currently on the NHSGGC database.

4.2.1 Inclusion criteria

Patients must meet the following inclusion criteria:

- Read or ICD coded diagnosis for asthma ever recorded
- Age ≥ 18 years two years prior to the index date
- ≥ 1 prescription for any of SABA, ICS, ICS/LABA combination in the two years prior to the index date
- ≥ 1 estimation of IgE in the two years prior to the index date

4.2.2 Exclusion criteria

Patients will be excluded from analyses if they have a Read or ICD coded diagnosis for any of the following:

- Hyper IgE syndrome (Job)
- Parasitic infection
- Allergic Bronchopulmonary Aspergillosis
- Churg Strauss / vasculitides
- Multiple myeloma
- Autoimmune disease

Patients will be excluded from analyses involving exacerbations if they have a Read or ICD coded diagnosis for:

- Bronchiectasis
- Interstitial lung disease

4.3 Study outcomes

Outcomes will be the tables and figures as listed in section 5.4.

4.4 Patient characterization

The following data will be captured:

- Age at index date
- Height
- Weight
- BMI
- Gender
- Smoking status
- Read or ICD code for allergy (assessed by at least 2 scripts for antihistamine in the last 12 months or by having a positive skin test or by in vitro reactivity to a perennial aeroallergen (cat, dog, house dust mite or other, (but not grass))
- Read or ICD code for COPD
- Read or ICD code for cardiovascular disease
- Read or ICD code for cerebrovascular disease
- Read or ICD code for diabetes mellitus
- Read or ICD code for depression
- Read or ICD code for osteoporosis
- Read or ICD code for bronchiectasis
- Read or ICD code for interstitial lung disease
- Read or ICD code for nasal polyposis

- Number of scripts for each of SABA, LABA, LAMA, ICS, ICS/LABA, montelukast, zafirlukast, theophylline, prednisolone <20mg/day DDD in the last two years prior to the index date
- Currently taking omalizumab (Xolair) or have been prescribed it in last two years prior to index date
- Number of exacerbations in two years prior to index date and the dates of the exacerbations (exacerbation defined by the number of courses of oral corticosteroids (defined as ≥20mg/day)
- Number of hospital admissions for asthma in the two years prior to index date and the dates of these admissions
- Number of A and E attendances for asthma in the two years prior to index date and the dates of these admissions
- Frequent exacerbator status (defined as those with ≥2 Rx for prednisolone ≥20mg DDD in the year prior to index date OR ≥ 1 hospital admission for asthma in the year prior to the index date)
- EOS count and date of measurement(s)
- IgE level and date of measurement(s)
- CRP level and date of measurement(s)
- Neutrophil count and date of measurement(s)
- Lymphocyte count and date of measurement(s)
- Platelet count and date of measurement(s)
- Compliance defined as a Medicines possession ratio (MPR) >80% where the MPR is the number of days of medication supplied within the refill interval divided by the number of days in the refill interval (from the NSHI look-up table)
- BTS step approximation (see table below)

BTS Step	
2	Those on ICS
3	Those on ICS plus LABA
4	Those on ICS + LABA + any of [tiotropium, LTRA, theophylline]
5	Those with ≥3 Rx for prednisolone <20mg in the last year (defined as chronic use) OR Current / ever taking Xolair / omalizumab therapy

5.0 Analyses

5.1 Software

All analysis will be carried out using IBM SPSS Statistics version 23.

5.2 Significance testing

Statistically significant results will be defined as p≤0.05.

5.3 Statistical analyses

5.3.1 Creation of new IgE and EOS variables

For each patient, there may be multiple measurements of both IgE and, particularly, EOS across the 2 years prior to the index date. Hence, the following new variables will be created for each of the two biomarkers:

IgE

- Maximum IgE in the two years prior to the index date
- An IgE >75 and ≤1500 at any time in the two years prior to the index date
- The number of measurements and the proportion of IgE levels >75 and ≤1500 in the two years prior to the index date
- The value of IgE corresponding to the same day measurement as EOS at any time in the two years prior to the index date

EOS

- Maximum EOS in the two years prior to the index date
- An EOS ≥400 at any time in the two years prior to the index date
- The number of measurements and the proportion of EOS levels ≥400 in the two years prior to the index date
- The value of EOS corresponding to the same day measurement as IgE at any time in the two years prior to the index date

5.3.2 Summary statistics and plots

Summary statistics will be produced for all patient characteristics. For variables measured on the interval or ratio scale, these include mean (standard deviation) or median (interquartile range is skewed), minimum and maximum, For categorical variables, the count and percentage by category will be presented.

Frequency plots will be used to illustrate the distribution of the continuous variables. Scatterplots will be used to assess the relationship between two continuous variables such as IgE and EOS.

5.3.3 Correlation analyses

Correlation coefficients will be used to assess the linear relationship between two continuous variables such as IgE and EOS (Spearmans correlation will be used if both variables are skewed and Pearson correlation if one or both variables are normally distributed).

5.4 List of dummy tables and figures

Figure 1: Patient flow diagram to illustrate the data identification process starting with the 1.4million patients in the NHSGGC database, excluding those with no valid IgE measurement in the two years prior to index date, excluding those with no Read or ICD code for asthma, excluding those aged less than 18 two years prior to index date, etc. The final line should show the number of patients eligible for analysis stratified by BTS step.

Table 1: Sociodemographic and medical characteristics of all asthma patients eligible for analysis. Note this will include weight where recorded and may include a composite definition of exacerbation as well as individual indicators.

Table 2: Sociodemographic and medical characteristics of severe asthma patients at BTS step 4 and above. Note this will include weight where recorded and may include a composite definition of exacerbation as well as individual indicators.

Table 3: Number of patients at BTS step 4 and above with EOS and IgE same day measurement

Table 4: Number of patients at BTS step 4 and above with prior, but not current, omalizumab / Xolair use

Figure 2: Distribution of IgE among those eligible for analysis overall and those in BTS step 4 and above

Figure 3: Distribution of EOS among those eligible for analysis overall and those in BTS step 4 and above

Figure 4: Distribution of IgE among those at BTS step 4 and above on regular prednisolone (defined as those with ≥3 Rx for prednisolone <20mg in the last year ie. chronic use)

Figure 5: Distribution of EOS among those at BTS step 4 and above on regular prednisolone (defined as those with ≥3 Rx for prednisolone <20mg in the last year ie. chronic use)

Figure 6: Descriptive statistics of the maximum IgE in the 2 years prior to index date overall and those in BTS step 4 and above

Figure 7: Descriptive statistics of the maximum EOS in the 2 years prior to index date overall and those in BTS step 4 and above

Figure 8: Scatterplot and correlation coefficient of maximum EOS versus maximum IgE among those BTS step 4 and above

Figure 9: Scatterplot and correlation coefficient of same day EOS versus same day IgE among those BTS step 4 and above

Figure 10: Scatterplots of maximum EOS by compliance with inhaled steroid medication (as assesed using the MPR) among patients BTS step 4 and above

Table 5: Number of patients at BTS step 4 and above by EOS/IgE combination group (high EOS/high IgE vs high EOS/low IgE vs low EOS/high IgE vs low EOS/low IgE). Define high IgE as >75 and high EOS as >400

Table 6: Characteristics of patients at BTS step 4 and above by EOS/IgE combination group (high EOS/high IgE vs high EOS/low IgE vs low EOS/high IgE vs low EOS/low IgE). Define high IgE as >75 and high EOS as >400

Table 7: Two way crosstabulation of how many patients BTS step 4 and above fulfill the criteria for Xolair by how many fulfill the possible criteria for reslizumab

Criteria for Xolair:

- continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year) [1]

- IgE level measured in the last two years >30 iu

- a positive skin test or in vitro reactivity to a perennial aeroallergen [1]
- (cat, dog, house dust mite, other but not grass)

Note: Due to lack of accessible electronic recording, spirometry data cannot currently be accessed through the Safe Haven

Criteria for reslizumab:

- Eosinophil level measured in last two years ≥ 400 cells

- Exacerbation rate. Pending guidance, presume continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)

6.0 Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study” and follows the ENCePP Code of Conduct (EMA 2014). The study will be registered with www.encepp.eu.

7.0 Data dissemination

A manuscript containing results and methodology will be submitted to a journal specialising in respiratory medicine. Data may also be presented in poster/oral form at appropriate medical conferences.

8.0 Study timelines

Action	Due date
Protocol finalised	31 December 2015
Funder sign off	Max 3 months
Data extraction	March 2016
Data review and statistics	April 2016
Report	9 May 2016
Investigator discussion	Mid May 2016
Final report	End May 2016
Manuscript	6-8 weeks from final report

9.0 Literature

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