Clinical utility of anti-interleukin 5 monoclonal therapy in asthma using a national, centralised, outcome-based system of drug access

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ABSTRACT

Introduction Interleukin 5 (IL-5) inhibitors are an important therapeutic advance in the management of severe, refractory, eosinophilic asthma. However, their utilisation should be targeted to maximise their benefits. This study used multisite, centralised, national data collected over 18 months to perform an observational integrated, retrospective, cohort study of selection criteria for initiation and continuation of IL-5 inhibitor treatment in Ireland.

Materials/patients and methods We used data from 230 patients who were given anti-IL-5 monoclonal therapy (reslizumab, mepolizumab or benralizumab) in Ireland between 2018 and 2020. Reimbursement of these drugs in Ireland requires fulfilling eligibility criteria defined by the Acute Hospitals Drugs Management Programme with continued reimbursement requiring ongoing submission of clinical data demonstrating clinical effectiveness.

Results IL-5 inhibitor use for 18 months was associated with a total reduction in asthma-associated hospital admissions of 108 (p=0.036) and in non-hospital exacerbations of 85 in 18 months (p=0.014). Respiratory-associated GP visits were reduced from 637 in 12 months to 89 at 6 months and 210 at 18 months of treatment (p<0.001). Oral corticosteroid requirement was reduced or stopped entirely (p<0.001). Subgroup analysis of one site replicated these results and showed a significant reduction in the Asthma Control Questionnaire Score (p<0.001)

Conclusions Selected patients continued on IL-5 treatment to 18 months had significantly reduced exacerbations, GP visits, oral corticosteroid use and asthma-associated hospitalisations. These results show that anti-IL-5 therapy, in carefully selected and monitored patients with asthma, results in significant improvements in clinical outcomes in a real-world setting.

INTRODUCTION

For patients with severe asthma whose symptoms remain uncontrolled and experience recurrent exacerbations, biological agents that target type 2 inflammation have been a significant advance. Most international guidelines now recommend that agents that target the interleukin (IL) 4/13 or IL-5 pathways be used as add-on treatment to maximum standard care.1 However, the high cost of these medications means that access is limited.2 One area of concern in access to the biologic agents is prior adherence to therapy. Patients who have been adherent to and continue to use inhaled corticosteroid/long-acting beta agonist treatment are most likely to benefit from these treatments. A number of trials and real-world studies have shown that IL-5 inhibitors benralizumab, reslizumab and mepolizumab have all been effective in significantly reducing numbers of asthma exacerbations and mean oral corticosteroid (OCS) use, and in improving average forced expiratory volume (FEV1) and Asthma Control Questionnaire (ACQ) Scores.3–7
In 2018, in order to increase equitable access to biologic agents that target the T2 pathway, a national programme of access was established. Access was based on a high exacerbation frequency in the previous 12 months and/or a requirement for continuous systemic steroids in the previous 6 months. Furthermore, eligibility required a detailed assessment of prior treatment adherence, inhaler training and asthma education. In this study we report a national prospective outcomes study of patients with severe asthma treated with anti-IL-5 therapy.

METHODS
Study subjects
All patients started on IL-5 inhibitor therapy through the national Acute Hospitals Drugs Management Programme (AHDMP) between 2018 and 2020 were included in this study. Patients eligible for treatment had to be over 18 years old and fulfil the eligibility criteria as per the Irish Health Service Executive (HSE) protocols. Patients who had previously received omalizumab treatment for their asthma and subsequently transitioned to an IL-5 inhibitor were excluded as their treatment was supplied under alternative funding schemes. Reasons for discontinuation were recorded.

Study design and methods
The study used data collected by AHDMP under a national prospective outcomes collection programme for IL-5-inhibitor treatments. The data consisted of information on 230 patients from 20 sites around Ireland over an 18-month period between 2018 to 2020. Specific clinical data capturing 12 months before and 12 months following commencement of IL-5 inhibitor treatment were collected at Cork University Hospital (CUH) from October to November 2021 in order to provide data not available in the national data set. This included specific recording of maintenance steroid use and ACQ Scores. The CUH site was chosen as it included one of the largest site cohorts of 21 patients and ACQ Scores are collected as part of routine clinical follow-up in CUH; hence the specific data required were readily available from the cohort of patients at this site.

Three IL-5 inhibitors were approved and in clinical use in Ireland during the period of data collection: benralizumab, reslizumab and mepolizumab. Treatment with each IL-5 inhibitor was administered per each product administration protocol. Details of patients who met the HSE eligibility criteria for IL-5 inhibitor treatment were submitted to ADHMP for approval for treatment. Patient demographics including confirmed non-smoker status, regular medication adherence, number of exacerbations requiring hospitalisation over 12 months, number of exacerbations requiring hospital visit but not hospitalisation over 12 months, number of general practitioner (GP) visits, baseline eosinophil levels and maintenance or treatment OCS use were obtained at baseline before commencing treatment and submitted to a central database managed by ADHMP. An exacerbation was defined as an increase in asthma symptoms requiring OCS treatment or an increase in maintenance OCS. Clinical outcomes following initiation of treatment were monitored at each clinical visit including exacerbations, hospitalisations due to exacerbations and GP visits with the data submitted to ADHMP to secure continued drug reimbursement. Response to therapy was reviewed by the treating physician at 3-monthly intervals. A definitive decision to continue therapy was made by the treating physician after 12 months of treatment, if not sooner, based on clinical response. Twelve months was determined as the cut-off in previous trials as benefit was measured in annual exacerbation rates. An adequate response was defined as: a clinically meaningful reduction in the number of asthma exacerbations requiring systemic corticosteroids or hospitalisation or clinically significant reduction in continuous OCS use while maintaining improved asthma control. Eosinophils were recorded pretreatment and post-treatment and analysed as a potential indicator of IL-5 treatment efficacy. Lung function test monitoring was not recorded at all sites at every visit and so was not included in the overall analysis.

Patient and public involvement
Due to the retrospective study design patients were not directly involved in the study design, although through open access the results will be widely available.

Data and analysis
Data were compiled prospectively by AHDMP and analysed retrospectively by an Irish Health Service Executive (HSE) statistician. Demographic information was not collected as a required variable but available demographics were sampled to determine a representation of age and gender breakdown. Only visits to the patient’s general practitioner pertaining to respiratory issues were included in the analysis. Since OCS use was documented as part of the data set and did not differentiate between maintenance OCS use and intermittent treatment course, OCS was analysed as a single set. Analysis of eosinophil levels was performed on 12-month data to provide a direct statistical comparison with the baseline 12-month data. The subanalysis of data from CUH analysis compared data for 12 months pre and post commencing IL-5 inhibitor treatment.

Analysis was performed in two parts. Descriptive analysis and an intention-to-treat pairwise analysis was performed on the full data set of 230 patients. A negative binomial mixed-effects model was used to account for the random effects inherent to unbalanced data sets. For the second analysis, a balanced data set was created using all patients (n=97) with a full set of 6-month, 12-month and 18-month data and excluded patients who had discontinued treatment or had not completed a full period of 18 months treatment. As the data were count data and demonstrated overdispersion (variance greater
Table 1 Documented reasons for discontinuation of IL-5 inhibitor treatment

| Reason for discontinuation                                      | Total |
|-----------------------------------------------------------------|-------|
| Recurrent intensive care unit (ICU) admissions (x 4)            | 1     |
| Adverse event—urticaria                                         | 1     |
| Lung cancer diagnosis                                           | 1     |
| Lack of efficacy                                                | 1     |
| Non-adherence, smoking, missed dose                             | 1     |
| Non-responder                                                   | 4     |
| Patient emigrated                                               | 2     |
| Patient refused to continue                                     | 1     |
| Switched to dupilumab                                           | 2     |
| Switched to omalizumab                                          | 1     |
| Planning pregnancy                                              | 1     |
| Death due to severe pre-existing cardiac disease                | 1     |
| Death due to pre-existing renal disease                         | 1     |
| Death due to sudden cardiac death (postmortem results still pending) | 1     |

Reason for discontinuation = documented reason for discontinuation of IL-5 treatment at any point during the 18-month treatment period.
Total = total number of patients discontinued on IL-5 inhibitor treatment for this documented reason.

RESULTS

Two hundred and thirty patients from 20 sites around Ireland were included in the analysis. Data were available for 191 patients who had received treatment for 6 months, 135 patients who had received treatment for 12 months, and 97 patients who had received treatment for 18 months at the time of analysis. The reasons for discontinuation of treatment are shown in table 1. Four patients died during the course of treatment but none attributable to IL-5 treatment. Five participants had the drug discontinued within the first 12 months of treatment by their treating physician due to lack of objective clinical response.

Descriptive analysis and an intention-to-treat pairwise analysis was performed on the full data set of 230 patients (table 2). Further pairwise analysis was performed on the cohort of 97 patients with 18 months of data for comparison of statistical rigour (table 3).

Sampling of the demographic information available showed a gender breakdown of 55% female and 45% male, with a median age of 57 years. The descriptive analysis showed the mean incidence of adverse effects due to severe uncontrolled asthma. Exacerbations were presented as those requiring hospitalisation and those which did not.

The mean number of exacerbations requiring hospital admission in the 12 months prior to starting IL-5 inhibitor treatment was 1.4 (n=230) and a total of 132 admissions. This had reduced to 0.21 (n=191) at 6 months with 84% (n=160) reporting no exacerbations requiring hospitalisation. This reduction was maintained at both 12 months (mean=0.28 (n=135)) and 18 months (mean=0.34 (n=97)). The mean number of community-treated exacerbations in the 12 months prior to starting IL-5 treatment was 1.09 per patient (n=230). At 6 months the mean reduced to 0.16 (n=191), 0.24 (n=135) at 12 months and 0.24 (n=97) at 18 months. At 18 months, 86% of patients reported no exacerbations in the 18 months after commencing therapy (n=83). Comparative analysis of these reductions for both hospitalisations and non-hospitalised exacerbations is shown in table 2.

GP visits were corrected for respiratory-associated visits, with a mean of 6.68 visits per patient to GP for respiratory-associated symptoms in the 12 months before starting IL-5 inhibitor treatment (n=230). This reduced to a mean of 0.83 visits at 6 months of treatment (n=191). At 12 months of treatment there was an average of 1.16 respiratory-associated visits over 12 months (n=135) and 2.16 visits in 18 months at 18 months of treatment (n=97). On comparison these reductions were all statistically significant (p<0.001).

The pairwise analysis of data at 18 months showed a direct comparison between the patient’s previous baseline (data from 12 months before starting IL-5 treatment) and their progress at 18 months (figure 1). There was a total of 132 hospital admissions due to exacerbation in the 12 months before starting treatment, which reduced to 10 admissions after 6 months of IL-5 treatment (p<0.001), 24 hospitalisations within 12 months (p=0.004) and 33 hospitalisations after 18 months of treatment (p=0.036). This was a total reduction of 99 hospitalisations over 18 months. For community-treated exacerbations, the 12 months pretreatment baseline was 109 exacerbations. At 6 months treatment there were 12 documented exacerbations (p=0.02), 19 exacerbations at 12 months (p=0.027) and 24 exacerbations at 18 months (p=0.014). GP visits started at a baseline of 637 visits in 12 months before IL-5 treatment. In the 18-month analysis this reduced to 89 visits at 6 months (p<0.001), 160 visits at 12 months (p<0.001) and 210 visits at 18 months (p<0.001). This was a total reduction of 427 GP visits in the 18 months of IL-5 treatment.

Descriptive analysis showed mean OCS use was 6.81 mg maintenance OCS per patient (n=152) in the 12 months prior to starting treatment, reducing to average maintenance OCS of 0.4 mg at 18 months (n=97, p<0.001). The 18-month data also showed this reduction was statistically significant at 6 months (p<0.001), 12 months (p<0.001) and 18 months (p<0.001).

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Comparative analysis of outcomes between benralizumab, reslizumab and mepolizumab showed no statistically significant difference in clinical outcomes between the different drugs (p<0.01). These data may have been skewed within the 18-month analysis population as only...
10 patients were documented on benralizumab with 36 on reslizumab and 36 on mepolizumab. Serum eosinophil levels at IL-5 inhibitor treatment commencement were analysed as a potential indicator of IL-5 treatment efficacy. Baseline eosinophil range was 260–2370 cells × 10^9/L with a mean of 780 cells × 10^9/L. High baseline eosinophil count was found to correlate with a higher rate of steroid reduction (p=0.03) but was not associated with other markers of treatment response.

The COVID-19 pandemic began during the data collection period in March 2019. This was a potential confounding variable as it caused national disruption to asthma admissions. Comparative analysis was run to assess potential measurable variance in data collected before the pandemic versus during the pandemic period, but no statistically significant variance was found (p=0.54).

For the subanalysis of data from CUH (table 4), 21 patients were assessed including 2 patients who were switched from reslizumab to mepolizumab during the treatment period. This switch was only performed for these specific patients due to physician direction when mepolizumab became available in Ireland. In the 12 months pre-IL-5 inhibitor treatment, there was a total of 160 documented exacerbations (mean=7.6, n=21) and 16 exacerbations requiring hospitalisation leading to a total of 128 hospital bed days. Fourteen patients were on maintenance OCS (5–25 mg) for asthma symptom control with an average dose of 11.7 mg. ACQ Scores ranged from 0.8 to 4.3 with an average of 2.9. After 12 months of IL-5 inhibitor treatment, this had reduced to five exacerbations requiring hospitalisation (p=0.016) with a total of 35 bed days (p=0.017, excluding 25 days for social admission), a total reduction of 11 admissions and 94 bed days.

There were only 18 documented non-hospitalised exacerbations, a total reduction of 142 (p<0.001). Sixteen patients required ongoing OCS treatment of 5-25mg of oral steroid at baseline, with an overall average dose of 11.7mg. Twelve of the 16 patients on maintenance oral corticosteroid were able to discontinue them completely at 12 months of IL-5 inhibitor treatment, with 4 patients maintained on their baseline OCS of 10-15mg. ACQ Scores reduced to 0.9(range 0–3.5, p<0.001) with 15 of the 21 patients improving to an ACQ Score of 1 or below.

### DISCUSSION

These results support the efficacy of IL-5 inhibitor treatment in appropriately selected patients. Side effects and adverse reactions were the only documented reasons for drug discontinuation, though still found to be minimal, with one reported case of urticaria and no other hypersensitivity reactions. All three of the IL-5 inhibitors included in the study appear to have equal efficacy, although there were insufficient data to conclusively determine this.

The high rates of symptom improvement demonstrate the important role of appropriate patient selection. The overall reduction in exacerbations in our study was greater than that reported in the individual trials for each drug. This difference could be due to our analysis using data at 18 months treatment while the trials used data from 24 months to 48 months, so the difference between results may potentially reduce with further analysis at 24 months or 48 months. However, our findings are also in keeping with existing real-world data including the recent UK real-world study which also used specific patient selection criteria and reported equivalent results, including a 72.8% reduction in exacerbations.
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with 48 weeks of treatment. These improvements are also significantly better than the trial data and potentially due to the specific selection criteria and close monitoring being used. Other real-world studies also found no statistically significant difference between outcomes of benralizumab and mepolizumab, though the use of selection

Table 4 Summary of subanalysis data from Cork University Hospital

|                          | 12 months pre-IL-5 treatment | 12 months IL-5 treatment | Mean |  Mean | P value |
|--------------------------|-------------------------------|--------------------------|------|-------|---------|
| Exacerbations            | 160                           | 18                       | 7.6  | 0.8   | p<0.001 |
| Exacerbations—inpatient  | 16                            | 5                        | 0.76 | 0.23  | p=0.016 |
| Bed days                 | 128                           | 35                       | 6.09 | 1.6   | p=0.017 |
| Maintenance steroid dose | 11.7 mg                       | 3.9 mg                   | 11.7 | 3.9   | p<0.001 |
| ACQ Score                | 2.8                           | 0.9                      | 2.8  | 0.9   | p<0.001 |

Exacerbations = number of recorded exacerbations (oral corticosteroid treatment/increase in maintenance oral corticosteroid dose for management) requiring specialist respiratory review but not requiring hospitalisation.
Exacerbations—inpatient = recorded exacerbations (increased asthma symptoms requiring antibiotic or corticosteroid treatment) requiring inpatient hospital treatment of at least 1 day.
Bed days = total number of days of hospital inpatient treatment due to exacerbation.
Maintenance steroid dose = average daily dose of oral corticosteroid required to maintain asthma symptom control.
ACQ Score = Asthma Control Questionnaire measure of asthma symptom severity, range 1–6.
12 months pre-IL-5 treatment = total number of events recorded within 12 months prior to starting IL-5 treatment.
12 months IL-5 treatment = total number of events recorded in the 12 months following commencement of IL-5 inhibitor treatment.
Mean = average number of documented events/treatment measure changes per patient during the stated time period.
P = P value probability significance measure.
The subgroup analysis of the CUH data provided greater specific detail of the real-world effects of IL-5 inhibitor treatments. The analysis showed that this cohort had more severe symptoms before starting IL-5 treatment than the national cohort, with a mean of 7.6 exacerbations in the 12 months before treatment in CUH compared with 1.9 nationally. The reductions in ACQ Score which were observed illustrate the clinical benefits gained by the patients. These results were in line with significant improvements in ACQ and ACT Scores in the previous trial and real-world data. These results also replicate the level of ACQ reduction found in previously published CUH reslizumab data which showed a mean ACQ-6 Score improvement from 3.5 at baseline to 1.7 at 1 year, and 2.0 at 2 years (p=0.0001). The significant reduction in OCS dosage has the potential to reduce the toxic side effects associated with long-term steroid use.

There are potential biases to our data which should be considered when reviewing these results. The most acute reduction in OCS use was noted at 6 months, with a slow upward trend in the 18-month data, though a significant overall benefit was maintained. A potential reason for this may be that aggressive weaning of maintenance OCS took place in most sites during the first 6 months of IL-5 inhibitor treatment as symptoms improved and the initial results of the first 6 months may have been influenced by this. The data after 6 months may be a closer reflection of intermittent OCS requirement while receiving IL-5 inhibitor treatment. Other considerations include the mode of IL-5 drug administration and frequency of administration which varied at some sites due to local arrangements and personal preference during the pandemic. Regarding the specific IL-5 inhibitors used, reslizumab was the first IL-5 inhibitor available in Ireland due to an early access programme, while benralizumab was only approved for reimbursement in Ireland in April 2019, partway through the data collection period.

Recent data published from the CHRONICL Study (Observational Study of Characteristics, Treatment and Outcomes With Severe Asthma in the United States) in the USA showed benralizumab caused a 58% reduction in asthma exacerbations in patients with severe asthma regardless of phenotype, though those with higher eosinophil levels did have a stronger response. Continued monitoring and development of the protocols in line with ongoing research and findings will allow targeted treatment to those who will gain the most benefit from it.

These results suggest that the current AHDMP guidelines have a strong predictive value to select appropriate patients who will gain significant benefits from these treatments. The close monitoring of clinical outcomes during treatment allows for those not gaining a clinical benefit to be moved to other treatments and increase capacity for new candidates to commence IL-5 inhibitor treatment. Unfortunately, as there are not sufficient data available regarding IL-5 use in Ireland prior to the introduction of the AHDMP guidelines, some comparisons remain difficult but may be addressed through the continuing collection of national outcomes. Previous research examining the clinical usefulness of the IgE inhibitor omalizumab in Ireland showed that despite the cost of the medication, reductions in exacerbations, hospital bed days and OCS use led to an overall significant reduction in healthcare burden and cost. We believe that a similar reduction in healthcare burden and cost is likely with appropriate use of IL-5 inhibitor therapy.

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