

Treatment and Outcomes in Patients with Asthma and Allergic Rhinitis in the United Kingdom

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Key Words

Asthma • Allergic rhinitis • Montelukast • Inhaled corticosteroids • Long-acting β -agonists

Abstract

Background: Since allergic rhinitis in asthma patients is associated with worse asthma control, the treatment of the comorbid condition may improve outcomes. **Methods:** A 1-year retrospective study using the UK Mediplus[®] database (2001–2004) included asthmatic patients aged 15–55 with allergic rhinitis. Patients starting therapy based on the Global Initiative for Asthma guidelines, defined as an increase in inhaled corticosteroids (high-dose inhaled corticosteroids, hdlCS), or the addition of montelukast (ICS+MON) or long-acting β -agonists (ICS+LABA) to ICS, were studied. Univariable and multiple logistic regressions evaluated asthma-related outcomes. **Results:** Among 2,596 asthma and allergic rhinitis patients, 83.2% initiated ICS+LABA, 12.1% hdlCS and 4.7% ICS+MON. The mean age was 34 years and 60% were female. ICS+MON patients had more moderate-severe asthma ($p = 0.04$). Approximately 84% of the ICS+LABA patients experienced an asthma control failure compared to 50% in the other groups ($p < 0.0001$). The proportions of patients requiring treatment change were 73.8, 22 and 27.3% in the ICS+LABA, hdlCS and ICS+MON groups, respectively ($p =$

0.001). Asthma-related resource use was similar among all groups. The ICS+MON group received fewer mean prescriptions for oral corticosteroids ($p = 0.024$) than the other groups ($p = 0.026$). **Conclusions:** In asthma and allergic rhinitis, treatment with ICS+MON or hdlCS was associated with lower rates of asthma control failure and fewer treatment changes than the ICS+LABA group. MON users also required fewer oral corticosteroids.

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Introduction

Asthma affects approximately 300 million people worldwide [1] and is most prevalent in industrialized nations, with noticeably high rates in the United Kingdom [2]. The most recent report from the Global Initiative for Asthma (GINA) indicates that the mean prevalence of clinical asthma in the United Kingdom and the Republic of Ireland is 16.1%, with a self-reported prevalence of asthma symptoms in adults ranging from 22% in England to 27% in Wales [3]. Recent studies of allergic rhinitis (AR) in Europe suggest that approximately 26% of all adults have clinical AR in the United Kingdom, and that as much as 45% of this population is undiagnosed [4, 5]. Furthermore, AR is considered a risk factor for allergic

asthma (A), and the two diseases are frequently presented comorbidly [6–8], with prevalence estimates of AR in asthmatics ranging from 28 to 100% [9].

In an earlier study assessing the effects of comorbid A+AR on outpatient and inpatient visits, drug use and costs, we showed that a concomitant diagnosis of AR significantly contributed to a greater number of outpatient visits, an increased likelihood of hospitalization, a greater number of prescriptions for short-acting β -agonists (SABA) and corticosteroids, and increased annual costs for asthma medications [10]. Several other studies confirm the link of comorbid A+AR with increased resource utilization and costs [9, 11, 12]. However, when AR is diagnosed and properly treated, not only are symptoms alleviated, but additional benefits may occur through a reduction of asthma-related complications [13–16], and potentially through an improved quality of life. These benefits are debatable though, due to heterogeneity in the methodological approaches of the studies evaluating the outcomes [17, 18].

Recently, treatment guidelines that address comorbid A+AR were developed by the Allergic Rhinitis and its Impact on Asthma Initiative (ARIA) in collaboration with the World Health Organization (WHO) [19]. These guidelines recognize the beneficial effect that AR treatment can have on asthma, and the potential overall cost reduction to society. Treatment for AR is recommended based on the type and severity of AR, and includes antihistamines and nasal corticosteroids, whereas treatment recommendations for asthma defer to the GINA guidelines. Montelukast (MON) is a single therapy available for the treatment of comorbid A+AR [20, 21] and current ARIA guidelines specify it as a treatment option.

The purpose of this study was to determine the treatment patterns for comorbid A+AR in patients with increased therapy in the United Kingdom as established by general practitioners (GPs). We also investigated asthma-related outcomes among independent asthma controller treatments: inhaled corticosteroids (ICS) and MON (ICS+MON), high-dose ICS (hdICS), or ICS and long-acting β -agonists (ICS+LABA).

Methods

Design and Data Source

Association between Allergic Rhinitis Status and Asthma Treatment Response (ASTAR) was a 1-year, longitudinal, retrospective cohort study utilizing data from the UK Mediplus® primary care database, containing nearly 1 million active patient records from a representative sample of approximately 500 GPs in

the United Kingdom. Routinely recorded clinical data from the standard election patient record have been collected for UK Mediplus since 1987, including demographic variables (age, gender) as well as medically relevant information including diagnosis, medical history, tests, GP visits, GP referrals and prescription drug use (dose and duration). Diagnostic codes are based on the READ coding system, adopted by the National Health Service for the United Kingdom. The Mediplus primary care database has been extensively validated and used in health services research [22]. A data analysis plan for this study was developed by all investigators and included a commitment to the publication of data.

Study Time Frame

This study included 2 treatment periods: a baseline period of 12 months prior to the index date and a follow-up period of 12 months after the index date. Patients were included if they fulfilled the relevant criteria within the index window of June 1, 2001 through May 31, 2003. If patients met the inclusion criteria, they were included on a specific index date and the data for that patient were evaluated 1 year prior to that index date (baseline) and 1 year after that index date (follow-up). As a result, the patients were evaluated over differing time periods, but all within the total study time frame between June 2000 and May 2004, and each patient over a 2-year period (see fig. 1).

Patient Selection

Patients were 15–55 years old and initiated a treatment of interest during the index period. Treatments of interest were defined as ≥ 2 prescriptions for hdICS, ICS+LABA or ICS+MON as suggested by the GINA step 3 therapy for uncontrolled asthma, written on 2 different dates during the 12-month follow-up period. hdICS designations were made based on the GINA guidelines [23], and patients in the ICS+LABA group were also permitted to be on a single-inhaler, fixed-dose combination treatment. Patients were designated as asthmatic via asthma diagnosis, defined by relevant READ codes, and treatment for asthma. Patients were also required to have comorbid AR, determined by either diagnosis or treatment. The diagnosis of AR was defined through the presence of relevant READ codes. The treatment of AR was defined as the presence of prescriptions for antihistamines, excluding competing conditions (i.e. urticaria or eczema) or nasal steroids, during the study period (June 2000 to May 2004). Patients were excluded if they had received any asthma controller treatment as specified by the GINA step 3 therapy during the 6 months prior to the index period, including antileukotrienes, LABA, hdICS or a combination of any of these. Patients were also excluded if they had a diagnosis of chronic obstructive pulmonary disease, emphysema, cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital respiratory disease, interstitial lung disease or tuberculosis. All treatment exposure groups were mutually exclusive.

Study Variables

The covariates assessed included the patients' age, gender, asthma severity and prior medication use. Asthma severity classifications were computed using a previously validated and tested two-step algorithm based on the number of SABA canisters and the number of oral corticosteroid prescriptions over a 1-year period [24, 25]. This index includes 4 categories: intermittent, mild

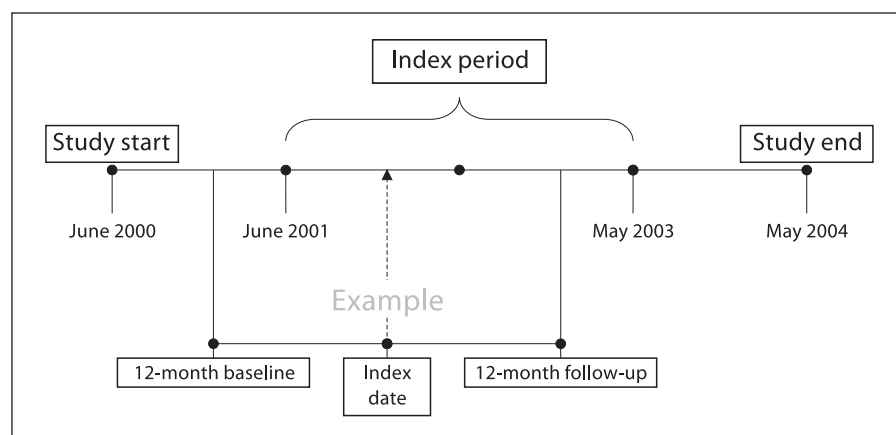


Fig. 1. Study time line.

persistent, moderate persistent and severe persistent asthma. Prior AR medication use, derived from baseline history, was categorized into 3 medication types: antihistamines only, nasal steroids only, and both antihistamines and nasal steroids. Due to the nature of the data, a complete and reliable lung function measure was not available, and therefore could not be included in the asthma severity classification. We were also unable to calculate oral corticosteroid dose ranges or mean daily or weekly SABA use due to the inconsistency of these data in the database as well as wide fluctuations on a per patient basis.

The outcome variables were asthma control failure, asthma treatment change and asthma-related medical resource use. An asthma control failure was defined by at least one of the following: an asthma-related emergency room visit, hospitalization, oral corticosteroid use, asthma treatment change, or at least an average of 1 SABA prescription per month. Asthma treatment change was characterized by either a switch to, an add-on of another asthma-related therapy, or both. Asthma-related medical resource use was measured by the number of hospitalizations or emergency room visits, the frequency of rescue medication use, i.e. SABA, and the frequency of acute medication use, i.e. oral corticosteroids or antibiotics used for lower respiratory tract infection.

Statistical Analyses

Descriptive statistics show the distribution of patients into the treatments of interest (ICS+MON, hdICS, ICS+LABA) and into baseline allergy treatment categories (antihistamines only, nasal steroids only, both antihistamines and nasal steroids). Univariable analyses comparing baseline characteristics and unadjusted outcome variables were conducted using t tests or Duncan's test for continuous data and χ^2 tests for categorical data. Multiple logistic regression models were developed to compare the effects of the treatments of interest (ICS+MON, hdICS, ICS+LABA) on outcomes (i.e. asthma control failure or asthma treatment change), controlling for age, gender, index prescription year, baseline allergy medication use and asthma severity. The model estimating asthma control failure was run twice, varying the definition of the SABA use parameter. In the base case analysis, SABA use was defined as previously described: 1 or more prescriptions per month. In the sensitivity analysis, SABA use was defined as 1 or more prescriptions per 3 months. Multiple regression models were de-

veloped to compare the effects of the treatments of interest on the mean number of SABA, oral corticosteroids and antibiotics used. Because the number of hospitalizations and emergency room visits was small, multivariable models were not suitable to estimate the effect on this variable. All data analyses were conducted using SAS, version 8.2 (Cary, N.C., USA). A two-tailed p value of 0.05 was considered statistically significant.

Results

Baseline Characteristics and Treatment Patterns

A total of 2,596 patients were selected for inclusion in the cohort (fig. 2). Of these, 1,591 (61.9%) were female and the mean age was 34.2 years. Additionally, 121 (4.7%) initiated treatment using ICS+MON, 314 (12.1%) were treated with hdICS and the remaining 2,161 (83.2%) were treated with ICS+LABA. Table 1 shows the baseline cohort characteristics of the treatment groups. The mean age of patients differed, with older patients more prevalent in the hdICS group ($p < 0.001$). Asthma severity was also different between the 3 groups, with more moderate and severe asthmatic patients identified in the ICS+MON group ($p = 0.04$).

Asthma-Related Outcomes

The mean and median doses of ICS per group are shown in table 2. Because dose-range specifications of medium or high vary according to drug type, we were unable to calculate a pooled mean for each respective treatment group. Patients in the hdICS dose received a mean of 1,270.8 μg of beclomethasone (median 1,500 μg), 1,463.5 μg of budesonide (median 1,600 μg) and 1,001.5 μg of fluticasone (median 1,000 μg). These doses were all significantly greater than those in either

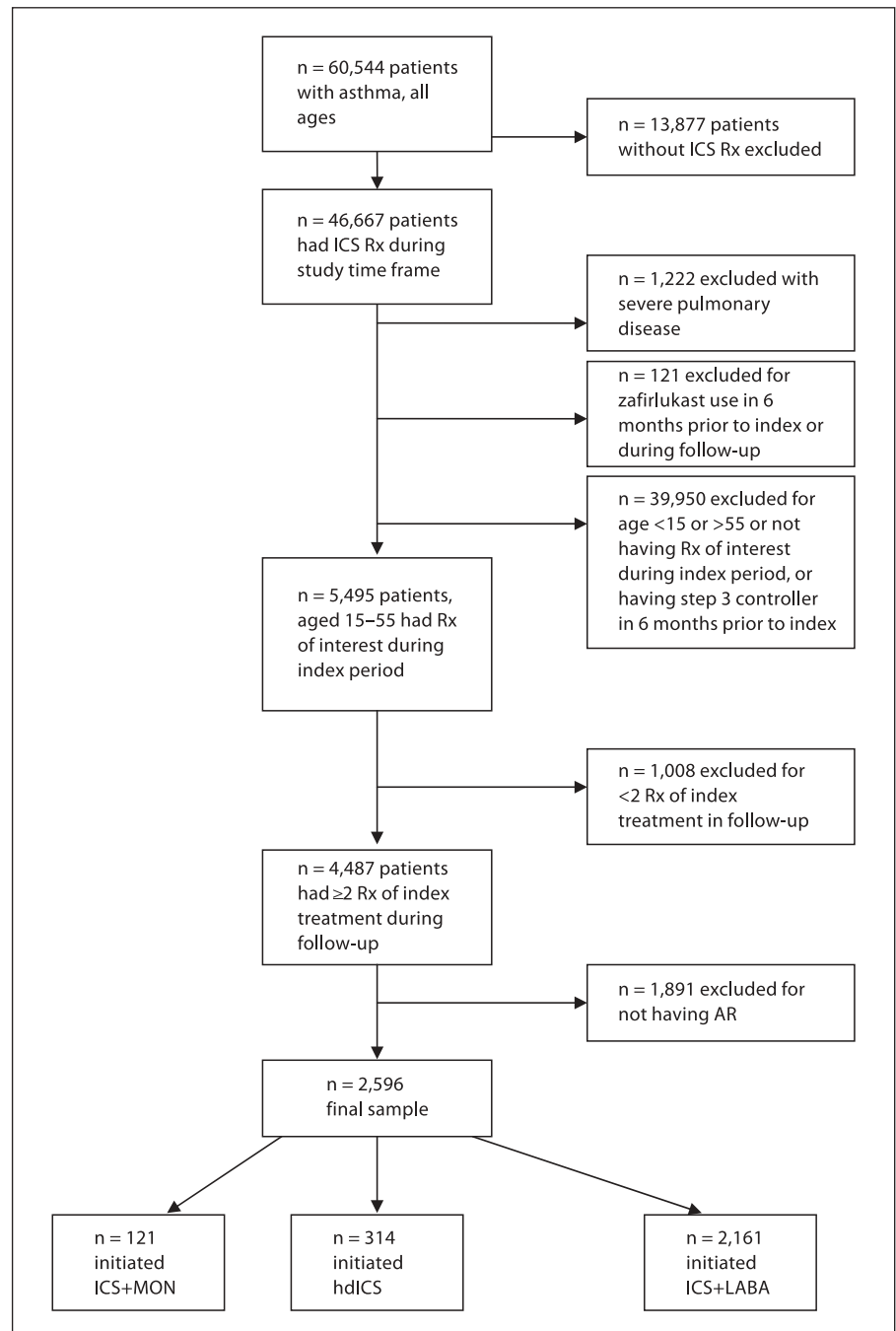


Fig. 2. Patient selection diagram. Rx = Prescription.

the ICS+MON or the ICS+LABA groups. The mean dose of budesonide was similar among the ICS+MON and ICS+LABA groups, although the mean dose of beclomethasone was significantly greater in the ICS+LABA group, while the mean dose of fluticasone was significantly greater in the ICS+MON group. Since the mean may be influenced by outliers, we also compared the me-

dian doses, which are similar among the ICS+MON and ICS+LABA groups for beclomethasone and fluticasone, though not for budesonide.

Patients in the ICS+LABA group were significantly more likely to have an asthma control failure than those in either the ICS+MON or hdICS groups ($p < 0.0001$). Approximately 50% of the patients in both the ICS+MON

Table 1. Baseline cohort characteristics

	ICS+MON	hdICS	ICS+LABA
Patients	121 (4.7%)	314 (12.1%)	2,161 (83.2%)
Mean age, years	32.4 ^b	36.6 ^a	34.0 ^b
Female	68 (57.6%)	186 (59.2%)	1,337 (62.6%)
Asthma severity ^{1, 2}			
Mild intermittent	16 (13.2%)	55 (17.5%)	437 (20.2%)
Mild	37 (30.6%)	122 (38.9%)	793 (36.7%)
Moderate	56 (46.3%)	109 (34.7%)	796 (36.8%)
Severe	12 (9.9%)	28 (8.9%)	135 (6.3%)
Prior ICS prescriptions, mean	2.16	1.77	2.19
Baseline allergy treatment			
Antihistamines	31 (25.6%)	53 (16.9%)	417 (19.3%)
Nasal steroids	13 (10.7%)	33 (10.5%)	231 (10.7%)
Antihistamines and nasal steroids	17 (14.1%) ^a	32 (10.2%) ^b	171 (7.9%) ^b

Figures with different alphabetic superscripts denote significant differences between groups derived using Duncan's test.

¹ Asthma severity defined by asthma severity algorithm [24] based on prescription history.

² Significant difference between categories based on homogeneity of distribution test.

Table 2. ICS doses (in µg) during 12-month follow-up

	ICS+MON	ICS+LABA	hdICS
ICS dose, mean ± SD ¹			
Beclomethasone	502.6 ± 249.3 ^a	575.6 ± 289.8 ^b	1,270.8 ± 577.4 ^c
Budesonide	714.9 ± 445.9 ^a	605.6 ± 266.3 ^a	1,463.5 ± 1,132.8 ^c
Fluticasone	645.4 ± 260.1 ^a	529.8 ± 297.8 ^b	1,001.5 ± 323.6 ^c
ICS dose, median (range) ²			
Beclomethasone	400 (100–1,000)	400 (100–2,000)	1,500 (100–2,000)
Budesonide	800 (100–2,000)	500 (100–2,000)	1,600 (400–6,000)
Fluticasone	500 (50–1,000)	500 (50–2,000)	1,000 (50–4,000)
<i>GINA recommended ICS dose ranges [23]</i>			
Steroid type	Low dose	Medium dose	High dose
Beclomethasone	200–500	500–1,000	>1,000
Budesonide	200–400	400–800	>800
Fluticasone	100–250	250–500	>500

Figures with different alphabetic superscripts denote significant differences between groups derived using Duncan's test.

¹ Mean dose ranges for ICS+MON and ICS+LABA fall within GINA specified guidelines for low to moderate dose inhaled beclomethasone and budesonide, and mean hdICS fall within the high-dose range. Mean doses may be affected by outliers, so we assessed medians. All median doses of inhaled corticosteroids fall within GINA guidelines.

² Statistical testing not conducted to determine significant differences among the medians.

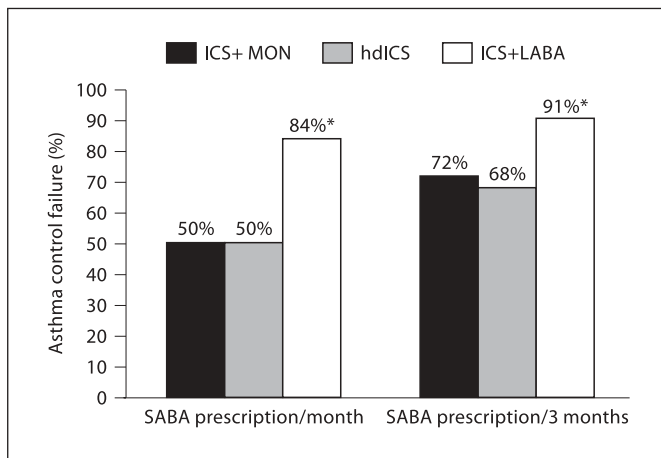


Fig. 3. Effect of treatment on asthma control failure. Asthma complication includes either asthma-related emergency room visit, hospitalization, oral corticosteroid use, asthma treatment change (switch/add-on/both) or ≥ 1 SABA prescription/month. Sensitivity analysis was performed with ≥ 1 SABA prescription/3 months. * $p = 0.001$.

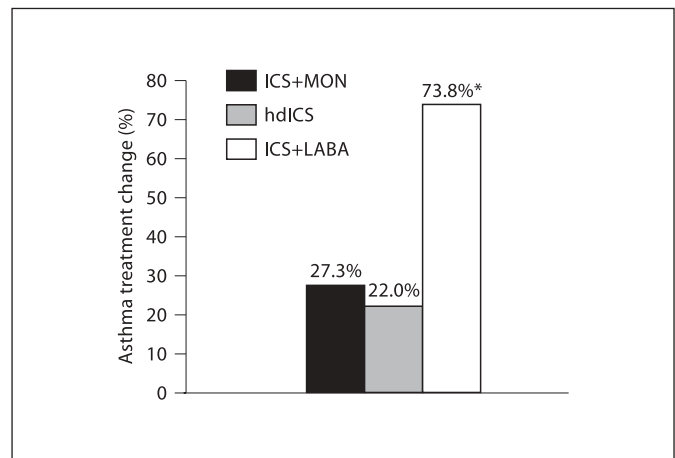


Fig. 4. Effect of treatment on asthma treatment change. Asthma treatment change is defined as addition of, or switch to another asthma medication, or both. * $p = 0.001$ between ICS+LABA and ICS+MON and between ICS+LABA and hdICS.

Table 3. Adjusted likelihood of asthma complication and asthma treatment change during follow-up

	ICS+MON	hdICS	ICS+LABA
Asthma complication ¹ (≥ 1 SABA prescription/month)			
Odds ratio (95% CI) ²	1 = ref. group	1.07 (0.69–1.66)	5.98 (4.03–8.89)*
Asthma complication ^{1,3} (≥ 1 SABA prescription/3 months)			
Odds ratio (95% CI) ²	1 = ref. group	1.15 (0.66–1.99)	6.67 (4.02–11.07)*
Asthma treatment change (switch/add-on/both)			
Odds ratio (95% CI) ²	1 = ref. group	0.76 (0.46–1.24)	7.76 (5.08–11.86)*

* Statistically significant difference from reference group (ref. group).
¹ Asthma complication includes either asthma-related emergency room visits, hospitalization, oral corticosteroid use, asthma treatment change (switch/add-on/both) or ≥ 1 SABA prescription/month.
² Multiple logistic regression analysis adjusting for age, gender, index prescription year, baseline allergy medication use and asthma severity.
³ Sensitivity analysis with ≥ 1 SABA prescription/3 months.

and hdICS groups experienced an asthma control failure, defined as emergency room visit, hospitalization, oral corticosteroid use, asthma treatment change or SABA prescription, compared with 84% in the ICS+LABA group ($p = 0.001$, fig. 3). The multiple logistic regression model shows that patients on ICS+LABA were nearly 6 times more likely (odds ratio 5.98, 95% CI 4.03–8.89) to have asthma control failure than those in the ICS+MON group (table 3). The sensitivity analysis provided similar results. When the definition of SABA use was modi-

fied to at least 1 SABA prescription every 3 months, the adjusted likelihood of having asthma control failure increased to be almost 7 times more likely for the ICS+LABA group than the ICS+MON group (odds ratio 6.67, 95% CI 4.02–11.07).

The proportions of patients receiving a treatment change were as follows: 27% of those in the ICS+MON group received a treatment change, compared with 22% in the hdICS and 73.8% in the ICS+LABA groups (fig. 4). As shown in table 3, the multiple logistic regression mod-

Table 4. Asthma-related medical resource use during 12-month follow-up (unadjusted)

	ICS+MON	hdICS	ICS+LABA
Patients	121 (4.7%)	314 (12.1%)	2,161 (83.2%)
Emergency room visits/hospitalizations			
Patients with ≥ 1 event	3 (2.5%)	4 (1.3%)	23 (1.1%)
Events, mean/patient	0.025 ^a	0.045 ^a	0.019 ^a
SABA use			
Patients with ≥ 1 prescription	108 (89.3%)	278 (88.6%)	1,827 (84.5%)
Prescriptions, mean/patient	5.64 ^a	4.33 ^b	4.46 ^b
Oral corticosteroid use			
Patients with ≥ 1 prescription	37 (30.6%)	98 (31.2%)	561 (26%)
Prescriptions, mean/patient	0.58 ^{a,b}	0.79 ^a	0.52 ^b
Antibiotics use (for LRTI)			
Patients with ≥ 1 prescription	7 (5.8%)	34 (10.8%)	160 (7.4%)
Prescriptions, mean/patient	0.06 ^b	0.12 ^a	0.08 ^{a,b}

LRTI = Lower respiratory tract infections.

^{a, b} Figures with different alphabetic superscripts denote significant differences between groups derived using Duncan's test.

el indicates that those in the ICS+LABA group were more likely to receive a treatment change than those in the ICS+MON group (odds ratio 7.76, 95% CI 5.08–11.86, $p < 0.0001$).

Asthma-Related Medical Resource Use

The overall number of emergency room visits and hospitalizations was small, so this prohibited multivariable analyses. In the unadjusted analysis (table 4) for these outcomes, patients in the ICS+MON group experienced a mean of 0.025 emergency room visits and hospitalizations compared with 0.045 in the hdICS and 0.019 in the ICS+LABA group, although these results were not significantly different. Similarly, the proportions of patients who received at least 1 SABA, oral corticosteroid or antibiotics prescription were not different. However, the mean number of SABA prescriptions per patient was greater in the ICS+MON group than in either of the other 2 groups ($p = 0.04$), whereas the mean number of oral corticosteroid prescriptions per patient was greater in the hdICS group than in the ICS+LABA group ($p = 0.005$), and the mean number of antibiotics prescriptions per patient was greater in the hdICS group than in the ICS+MON group ($p < 0.05$).

The above-noted differences disappeared when covariates were added. In the adjusted analyses, there were neither any statistical differences in the mean number of SABA prescriptions nor in the mean number of antibiotic prescriptions written for each respective treatment group. Similarly, the likelihood of receiving SABA, anti-

biotic or oral corticosteroid prescription during the follow-up period did not differ among the 3 groups (table 5). However, patients treated with ICS+MON received fewer prescriptions for oral corticosteroids than those in the hdICS ($p = 0.026$) and ICS+LABA ($p = 0.024$) groups.

Discussion

This retrospective cohort study included 2,596 patients with comorbid A+AR. Of these, 4.7% were treated by adding MON to ICS, 12.1% were treated with an increased dose of ICS, and 83.2% were treated by adding LABA to ICS. We demonstrated that patients treated by adding MON to ICS were less likely to suffer from an asthma control failure and less likely to receive a medication change compared with those treated by adding LABA. Asthma control failure and asthma treatment change were similar in the 2 groups to which MON was added and the ICS dose was increased, suggesting that these treatments result in similar outcomes in the regular clinical practice setting. Asthma-related resource use was similar among all 3 groups, apart from a lower use of oral corticosteroids in patients treated by adding MON to ICS.

Clinical trials have confirmed the safety and efficacy of MON in adults with asthma [21, 26, 27]. In patients with comorbid A+AR, clinical trials have demonstrated the benefit of MON compared with placebo, ICS and LABA in addition to ICS [11, 20, 28–30]. In a post hoc

Table 5. Adjusted likelihood and mean asthma-related medical resource use during 12-month follow-up

	ICS+MON	hdICS	ICS+LABA
SABA use			
≥ 1 prescription/year, odds ratio (95% CI) ¹	1 = ref. group	1.41 (0.58–3.39)	0.96 (0.44–2.09)
Parameter estimate ²	ref. group	–0.46; NS	–0.13; NS
Oral corticosteroid use			
≥ 1 prescription/year, odds ratio (95% CI) ¹	1 = ref. group	1.21 (0.72–2.04)	1.25 (0.78–1.98)
Parameter estimate ²	ref. group	0.30; p = 0.026*	0.27; p = 0.024*
Antibiotics (for LRTI) use			
≥ 1 prescription/year, odds ratio (95% CI) ¹	1 = ref. group	2.06 (0.87–4.85)	1.54 (0.69–3.44)
Parameter estimate ²	ref. group	0.06; NS	0.03; NS

Hospitalizations/emergency room visits were very rare. Hence, adjusted analysis using multivariate models could not be executed. LRTI = Lower respiratory tract infections; NS = not statistically significant ($p \geq 0.05$); ref. group = reference group.

* Statistically significant difference from reference group.

¹ Based on multiple logistic regression analysis adjusting for age, gender, index prescription year, change in asthma therapy, baseline allergy medication use and asthma severity.

² Based on β hat value from multiple linear regression analysis adjusting for age, gender, index prescription year, change in asthma therapy, baseline allergy medication use and asthma severity. Negative values signify a lower use than in the reference group, positive values a higher use than in the reference group. The parameter estimate reflects the difference in mean prescriptions between the groups.

analysis of the COMPACT clinical trial [21], patients with A+AR had a greater increase in lung function after adding MON to budesonide 800 μ g/day compared to those subjects for whom the dose was doubled [28]. In a separate trial, Bjermer et al. [26] showed that the addition of MON to ICS was at least equivalent to adding LABA to ICS in typical clinical measures. A post hoc analysis of these data showed a lower resource use and a decrease in allergy medication use for those with A+AR treated by adding MON to ICS, although these results were not statistically significant [11]. In contrast, Nathan et al. [17] have shown fluticasone nasal spray to be superior to MON in a 12-week study, while Dahl et al. [18] have shown that both inhaled and intranasal fluticasone are required to control seasonal symptoms of A+AR, over a 4-week period.

While there have been several observational studies conducted on health-related outcomes in asthmatic patients treated with MON and ICS [31–38], little observational evidence exists for patients with A+AR [31, 38, 39]. In a study assessing asthma control and resource use in Italy, Poland and Spain, Borderias et al. [39] have shown significant reductions in asthma attacks, SABA and oral corticosteroid use, as well as reductions in outpatient and inpatient visits when A+AR patients were treated with ICS and MON. In all 3 countries, the mean annual costs

of outpatient, emergency room and inpatient visits were significantly reduced in those treated by adding MON to ICS, as was the total annual direct cost [40]. In the pre-post analysis of the PEDIANET database in Italy by Sturkenboom et al. [38], the rates of asthma exacerbations as well as rescue and oral corticosteroid medication use were evaluated. Children in the A+AR subgroup ($n = 88$), were less likely to experience asthma exacerbation (adjusted odds ratio 0.15, 95% CI 0.02–1.26), although this difference was not significant. Travier et al. [31] conducted a pre-post analysis showing that the subgroup of A+AR children received significantly fewer total mean prescriptions for concomitant asthma and allergy medications than those on therapies ($p = 0.013$) where LABA was added to ICS or the ICS dose was increased. This difference in resource use led to lower costs for the MON and ICS group versus a significant increase in costs for the other therapies.

The clinical trial and observational evidence discussed above suggest that adding MON to ICS may be beneficial in patients with A+AR. However, no study to date has compared the outcomes in adult patients with A+AR in regular clinical practice. Our study is the first observational study to assess treatment patterns and outcomes in this population. The following treatment pattern is worth noting.

GPs prescribe the addition of MON to ICS more frequently to more severe asthma patients. This prescribing pattern may suggest that physicians perceive that the addition of MON provides more adequate control for moderate-severe asthma patients in practice or perhaps that patients who have failed to achieve good asthma control by adding LABA to ICS are then switched to treatment with MON. It is difficult to speculate why GPs in the United Kingdom prefer one treatment over another, however, our results do suggest that although GPs prescribe LABA in addition to ICS more frequently than any other treatment for GINA step 3 patients, adding MON to ICS may be more beneficial to a greater number of patients than those for whom it is currently prescribed. Although we have not specifically assessed costs, we have shown that the resource use of patients on all 3 therapies is similar.

The use of the Mediplus database has contributed to the strength of this study through its size and representative nature. However, this is a retrospective analysis, and therefore prohibits a randomization of patients into treatment groups. Although we adjusted for the lack of randomization in the statistical analysis, randomized studies are generally considered the 'gold standard' when comparing different treatments. Yet, there are advantages to conducting large observational studies such as this one. These include the ability to observe a more heterogeneous sample which may be more representative of the actual population, a long-term outcome measurement which can differ from short-term data in a seasonal disease like A+AR, and the ability to measure actual adherence patterns [38, 41, 42]. Finally, by retrospectively capturing the assignment of patients into specific treatment groups we were able to show treatment patterns of GPs and, potentially, how the most common treatment (ICS+LABA) may not be the only option for patients with A+AR.

An additional limitation of the study is the variation of dose ranges across the treatment groups. We used data from the follow-up period to calculate the mean ICS doses for all groups. Because patients in all 3 groups experienced asthma treatment change or asthma control failure, at some point in the study period these patients would have increased their respective doses of medication for at least a short period of time. This increase in doses would have been reported as asthma treatment change or asthma control failure and therefore explains the large standard deviations presented. It is also worth noting that recent studies have suggested that some patients may receive inflated ICS doses in practice, and these large deviations from the recommended dose may reflect this

pattern [43]. Considering that these outliers may have influenced the mean values, we also report the medians, which tend to be better markers for skewed data. As can be seen by the medians, the hdICS group received hdICS according to the GINA guidelines and those in the LABA and MON groups received low to medium ICS doses according to the GINA guidelines in a similar manner. Thus, although differences in doses may affect treatment outcomes, it appears that the differences we were able to ascertain are negligible and reflective of the heterogeneity of treatment regimes for the adult A+AR population.

The assumption that a filled prescription constitutes compliance may be a source of bias that could lead to an overestimation of the actual rate of medications taken in this study. Since this would likely occur on a random basis, the bias would more than likely be distributed across the treatment groups and would not affect the assessment of the treatments in comparison with one another. Additionally, prescription refills have been validated as acceptable proxies for comparative compliance in large database studies [44].

Generally, asthma patients appear to be more compliant with oral medications versus inhaled medications [45], and this could bias the results of this study in favor of montelukast. However, in the aforementioned systematic literature review, Bender and colleagues [in press] also claim that when dosing frequency is increased to more than two times per day, compliance decreases. In our study, patients took either high dose ICS or long acting beta agonists in addition to ICS twice per day. In contrast, montelukast users took ICS twice per day as well as the oral tablet once at night. Whereas patient preference for the oral formulation could lead to better compliance, it could be argued that the increased complexity of the montelukast regimen may decrease compliance with the ICS component of their treatments. Therefore, it is not likely that preference for a certain formulation would disproportionately affect treatment compliance in this study.

The identification of asthma severity continues to pose challenges with retrospective studies [46]. Because we used a previously published algorithm for asthma severity and controlled for asthma severity in the analyses, we have accounted for this bias to the best of our abilities. Similarly, the use of antibiotics as a proxy for acute medication use may be viewed as problematic because antibiotics may have been prescribed for conditions other than lower respiratory tract infection. We attempted to account for this potential bias by cross-verifying the prescription of antibiotics with the READ diagnostic codes

provided by the GP on the same day for which the prescription was written.

Finally, we were limited by the fact that AR was identified either by diagnosis or prescription for AR-related medications because over-the-counter medication usage is not included in the Mediplus database. Since many patients have undiagnosed comorbid A+AR, they may utilize over-the-counter medications rather than prescription medications [19], which would exclude them as AR patients in the Mediplus database. As a result, those included in this study may represent a more severe population. The potentially increased severity of AR may lead to poorer overall health outcomes, which may lead to a greater marginal treatment effect. Because all patients included in this study had AR, the distribution of severity would likely be random and would therefore not disproportionately affect the comparisons across treatments. It is also important to note that the numbers of A+AR patients in this study may be lower than in the actual population because we may have missed undiagnosed or less severely affected patients. Therefore, the results of this study may not be generalizable to asthma patients with milder forms of AR. However, these results do highlight the need for treating the comorbid condition as indicated in the ARIA guidelines [19].

In conclusion, we have confirmed the findings of other researchers who have demonstrated an association between the use of ICS and MON with a reduction in asthma complications and treatment changes. We have confirmed a significant reduction in the use of oral corticosteroids for those receiving ICS and MON. By reduc-

ing the cumulative negative effects that steroids may have, treatment with MON and ICS may provide a safer alternative for some patients. In the United Kingdom, the treatment of patients with A+AR using ICS and MON is as beneficial as increased doses of ICS, and may be more beneficial than the treatment with ICS+LABA.

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