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To cite this article: Jina Shin, Seung-Jun Oh, Tanaz Petigara, Kaan Tunceli, Eduardo Urdaneta, Prakash Navaratnam, Howard S. Friedman, Sung Woo Park & Song Hee Hong (2019): Comparative effectiveness of budesonide inhalation suspension and montelukast in children with mild asthma in Korea, Journal of Asthma, DOI: [10.1080/02770903.2019.1648504](https://doi.org/10.1080/02770903.2019.1648504)

To link to this article: <https://doi.org/10.1080/02770903.2019.1648504>

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Comparative effectiveness of budesonide inhalation suspension and montelukast in children with mild asthma in Korea

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ABSTRACT

Objective: The comparative effectiveness of low-dose budesonide inhalation suspension (BIS) versus oral montelukast (MON) in managing asthma control among children with mild asthma was assessed in Korea.

Methods: Claims from Korea's national health insurance database for children (2–17 years) with mild asthma (GINA 1 or 2) who initiated BIS or MON during 2015 were retrospectively analyzed. Pre- and post-index windows were 1 year each. Adherence, persistency, asthma control, asthma-related health-care resource utilization, and costs were evaluated using unadjusted descriptive statistics and propensity score-matched regression analyses.

Results: The number of children identified was 26,052 for unmatched ($n = 1,221$ BIS; $n = 24,831$ MON) and 2,290 for matched populations ($n = 1,145$ per cohort). Medication adherence, measured by proportion of days covered, was low for both cohorts but significantly higher for MON versus BIS (13.8% vs. 4.5%; $p < .001$). Time to loss of persistency was longer for MON versus BIS (82.3 vs. 78.4 days, respectively; $p < .001$). Mean number of post-index asthma-related office visits was 6.6 for BIS versus 8.3 for MON ($p < .001$). However, a greater proportion of patients in the BIS cohort had an asthma exacerbation-related office visit than the MON cohort (78.3% vs. 56.1%; $p < .001$). Asthma-related total health-care costs were higher with MON versus BIS (₩ 190,185 vs. ₩ 167,432, respectively; $p < .001$), likely driven by higher pharmaceutical costs associated with MON (₩ 69,113 vs. ₩ 49,225; $p < .001$).

Conclusions: Montelukast patients had better adherence, a longer time to loss of persistency, and were less likely to experience an exacerbation-related office visit in the post-index period than BIS patients.

ARTICLE HISTORY

Received 26 November 2018

Revised 20 June 2019

Accepted 21 July 2019

KEYWORDS

Adherence; persistency; asthma control; health-care resource utilization; cost

Introduction

Asthma is the most common chronic respiratory disease worldwide with an estimated prevalence of 358 million people (1). Multi-country cross-sectional surveys in the Asia Pacific region (2) show that while the prevalence of asthma is growing, asthma control is suboptimal, with significant overuse of short acting beta-agonists (SABAs) across asthma severities and significant underuse of guideline-recommended controller agents such as inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) (2–5). In South Korea, the proportion of patients reporting well-controlled asthma was only 8% when evaluated

against GINA criteria (3). In the landmark Asthma Insights and Reality in Asia-Pacific (AI-RIAP) household interview and survey study, ICS usage was lowest in South Korea with only 1.2% of asthmatics using an ICS agent (5). To the contrary, the majority of patients were using short-acting beta-agonists (SABA; 56.3%) to manage their asthma, irrespective of a severity level (5).

Oral formulations such as montelukast (MON) may offer a more convenient treatment option for pediatric patients than ICS. As per GINA treatment guidelines, ICS and MON are both recommended controller agents to manage mild asthma among

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children (4). Given that there is a lack of “real-world” evidence on the comparative use of LTRA agents versus ICS agents among children in Korea, there is a need to conduct a comparative effectiveness study of BIS versus MON, two frequently used agents for each of these medication classes, for the control of mild asthma in Korea.

ICSs reduce airway hyperresponsiveness and have anti-inflammatory effects, resulting in effective asthma control (6). LTRAs block leukotrienes which are involved in airway smooth muscle contraction, vascular permeability, mucus production, and airway inflammation (6). GINA guidelines recommend ICS as the preferred treatment for mild, persistent asthma with LTRA as an initial controller option for some patients who are unable or unwilling to use ICS or who cannot tolerate ICS (4). The US National Heart, Lung, and Blood Institute concluded that in head-to-head clinical trial comparisons of ICS agents versus LTRA monotherapy, ICS agents had a better clinical efficacy against asthma-related patient outcomes under controlled clinical conditions (6). However, most of the head-to-head trials used to draw this conclusion were for ICS inhalers (6). Of interest is the comparison between LTRA and nebulized administration of suspension ICS for children.

Nebulized administration of suspension ICS enables administration of accurate doses without placing the patient at risk of over- or under-dosing. This is especially important for vulnerable populations such as children who may be unable to correctly self-administer or accept inhaler devices. On the other hand, nebulized ICS is much more time-consuming (approximately 10 min) (7) than administration by inhalers. Twice-daily nebulizer treatments may be a burden on caregivers, impacting adherence and subsequent asthma control.

The number of head-to-head studies specifically comparing low-dose budesonide inhalation suspension (BIS) and orally administered MON in mild asthmatic children is sparse. Some studies have shown a marginal positive impact on asthma control outcomes that favors BIS over montelukast (8–10). In a 52-week comparative study of BIS and MON in young children (aged 2–8 y) with mild persistent asthma, Szeffler et al. (10), demonstrated that while there was no difference between the two agents in time to severe exacerbation events, there was a longer time to augmentation with another controller agent at 12 weeks ($p=0.050$) and a lower exacerbation event rate at 52 weeks ($p=0.034$) with BIS compared with MON. In a post-hoc subanalysis of this study focusing on younger patients (aged

2–4 y), while there were no differences in time to asthma controller medication augmentation between BIS and MON (primary efficacy end-point), there were additional secondary end-points (such as concomitant oral steroid use, number of additional controller medication use, etc.) where BIS was shown to be superior than MON (11). However, these studies were conducted under controlled conditions where treatment adherence and persistency were tightly managed. It is not known whether these findings can be extended to real-world settings where treatment adherence and persistency are known to be suboptimal, like in Korea (12,13).

This comparative effectiveness study aimed to evaluate medication adherence and asthma control outcomes among pediatric patients with mild asthma in Korea who were initiated with MON or nebulized ICS. Medication adherence was measured in terms of treatment adherence and treatment persistency while asthma control outcomes were measured in terms of medication augmentation and exacerbation-related health-care resource utilization. All-cause and asthma-related total health-care resource utilization and costs were further examined in children with mild asthma managed with either MON or low-dose BIS in real-world settings in Korea.

Methods

This was a retrospective, observational cohort study conducted in 2017 using national health insurance claims data from the Health Insurance Review and Assessment (HIRA) Service. South Korea has a universal health insurance system covering approximately 98% of the population. The HIRA database contains patient demographics, medical diagnosis codes, treatment and procedure codes, prescriptions, health-care utilization and cost data from both inpatient and outpatient settings. The database covers almost 80,000 health-care service providers and 99% of all medical institutions in Korea. Claims for approximately 46 million patients are received each year, representing 90% of the total population (14,15). The observation period for this study included 3 years of longitudinal claims data from January 1, 2014 to December 31, 2016. The patient identification period was 1 year from January 1, 2015 to December 31, 2015 (Supplemental Figure E1).

Institutional Review Board approval was obtained as part of the HIRA data access application (IRB No. E1707/003–004).

Study population

The study population included children diagnosed with mild, persistent asthma (as defined by GINA Step 1 or 2 treatment guidelines) (4) and treated with either MON or low-dose BIS monotherapy. Patients eligible for the study were between the ages of 2 and 17 years during the identification period; had at least two distinct office visits separated by at least 7 days with a primary or secondary diagnosis of asthma (ICD-10 CM code J45), or an emergency room (ER) visit with a primary or secondary diagnosis of asthma, or an inpatient hospital stay with a primary or secondary admission diagnosis of asthma; had at least two prescription records of either low-dose BIS (≤ 500 mcg budesonide per day) or MON associated with a primary diagnosis of asthma; and had at least 2 years of longitudinal follow-up (1 year pre-index and 1 year post-index). The earliest date of the first MON or low-dose BIS prescription record constituted the index date for the study.

Patients were excluded if they were classified under GINA Steps 3 through 5[4] during the pre-index period inclusive of the index date or if they had used any controller medications in the 30 day pre-index window exclusive of the index date. If prescriptions were written for either medium- or high-dose ICS, or for a combination of two controller agents such as ICS/long-acting β -agonists and low-dose ICS/LTRA, patients were classified as meeting the conditions of GINA Step 3 through 5.

Outcomes

Patient demographics, clinical characteristics, medication use, health-care resource utilization, and costs were collected in the pre-index period for both cohorts. In the post-index period, treatment adherence, treatment persistency, asthma control, health resource utilization, and costs were compared between the MON and low-dose BIS cohorts, using both unadjusted descriptive statistics and adjusted multi-variable analyses.

Adherence

Medication adherence was assessed using a percentage of the days' covered (PDC) calculation. The PDC was calculated as the total days' supply (accounting for overlaps) of the index treatment (MON or BIS) within the observation period of interest, expressed as a percentage.

Persistency

Treatment persistency was based upon changes in index asthma medication due to discontinuation, switching or start/re-start. Patients were assumed to be persistent if they did not experience any discontinuation, switching or start/re-start during the post-index observation period.

Discontinuation was defined by the identification of a medication gap of at least 1.5 times the days' supply of the preceding record of fill with no other recorded fills of the index treatment (MON or BIS) through the end of the post-index observation period. Switching events were assessed by the identification of no additional fills of the index treatment (MON or BIS) within a permissible medication gap of 1.5 times the days' supply of the preceding record of fill with no other recorded fills of the index treatment but with a record of fill of another asthma controller agent within the post-index observation window. Start/re-start events were defined by the identification of no additional fills of the index treatment (MON or BIS) within a permissible medication gap of 1.5 times the days' supply of the preceding record of fill, with a re-initiation of the index treatment beyond this permissible medication gap within the post-index observation window. For situations in which the record of the preceding days' supply had either no days' supply or a suspiciously low days' supply, the population median days' supply was used as a substitute. The duration of medication gaps and time to the first loss of persistency were also analyzed in both cohorts.

Indicators of asthma control

Medication augmentation and exacerbation-related health-care resource utilization were examined as indicators of asthma control. Medication augmentation was defined as the addition of any controller agent (e.g., ICS, ICS/long-acting β -agonist, mast cell stabilizer, or other LTRA) to the original MON or BIS prescription, the addition of MON to index low-dose BIS and vice versa, dose escalation of index treatment (MON or BIS), or more than one recorded prescription for SABA (1 canister of 200 doses) over 100 days. Exacerbation-related health-care resource utilization was defined as an asthma-related office visit, asthma-related ER visit, or an asthma-related hospitalization in conjunction with administration of nebulized SABA or intravenous injection of a corticosteroid or oral corticosteroid (OCS) within 5 days of the visit. Asthma control indicators were tracked in the post-index period and reported at distinct 3-month time windows (i.e., 0–3, 4–6, 7–9, and 10–12 months) as well as cumulatively at 3, 6, 9, and 12 months. Since

Table 1. Baseline characteristics.

	Unmatched population			Matched population		
	BIS cohort	MON cohort	p-value	BIS cohort	MON cohort	p-value
Total, n	1,221	24,831		1,145	1,145	
Sex, n (%)			.063			.799
Female	498 (40.8)	10,798 (43.5)		466 (40.7)	472 (41.2)	
Male	723 (59.2)	14,033 (56.5)		679 (59.3)	673 (58.8)	
Age						
Total, mean years (SD)	5.4 (3.4)	6.6 (3.8)	<.001	5.5 (3.4)	5.2 (3.2)	.190
≤5 years, n(%)	762 (62.4)	11,798 (47.5)	<.001	708 (61.8)	731 (63.8)	.320
>5 years, n(%)	459 (37.6)	13,033 (52.5)		437 (38.2)	414 (36.2)	
Insurance Type, n(%)			.028			.300
Health insurance	1,201 (98.4)	24,169 (97.3)		1,125 (98.3)	1,131 (98.8)	
Medical aid (for individuals below poverty level)	20 (1.6)	662 (2.7)		20 (1.8)	14 (1.2)	
Comorbidities, n(%) (pre-index)						
Pneumonia	444 (36.4)	6138 (24.7)	<.001	424 (37.0)	438 (38.3)	.546
Influenza	161 (13.2)	2755 (11.1)	.024	150 (13.1)	160 (14.0)	.541
Allergic rhinitis	1076 (88.1)	23,000 (92.6)	<.001	1005 (87.8)	1019 (89.0)	.361
Contact dermatitis and related conditions	354 (29.0)	7298 (29.4)	.766	333 (29.1)	355 (31.0)	.316
Atopic dermatitis and other eczema	680 (55.7)	12,779 (51.5)	.004	643 (56.2)	660 (57.6)	.473
Urticaria	366 (30.0)	6176 (24.9)	<.001	351 (30.7)	364 (31.8)	.558
Inflammatory bowel disease	221 (18.1)	4035 (16.3)	.088	209 (18.3)	224 (19.6)	.423
Chronic sinusitis	292 (23.9)	6109 (24.6)	.586	277 (24.2)	260 (22.7)	.402
Acute sinusitis	597 (48.9)	13,599 (54.8)	<.001	581 (50.7)	602 (52.6)	.380
Otitis	549 (45.0)	10,427 (42.0)	.040	519 (45.3)	570 (49.8)	.033
Provider characteristics (on index date)						
Institutional type, n(%)			<.001			.002
Advanced general hospital (tertiary)	0 (0.0)	234 (0.9)		0 (0.0)	14 (1.2)	
General hospital (secondary)	45 (3.7)	516 (2.1)		44 (3.8)	35 (3.1)	
Hospital (secondary)	32 (2.6)	2654 (10.7)		32 (2.8)	29 (2.5)	
Senior care hospital (secondary)	0 (0.0)	8 (0.0)		0 (0.0)	0 (0.0)	
Clinic (primary)	1144 (93.7)	21,417 (86.3)		1069 (93.4)	1067 (93.2)	
Public health center (primary)	0 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)	
Public health hospital (primary)	0 (0.0)	1 (0.0)		0 (0.0)	0 (0.0)	
Provider specialty, n(%)						
Pediatrics	607 (49.7)	12,392 (49.9)	<.001	600 (52.4)	642 (56.1)	.364
Internal medicine	260 (21.3)	9231 (37.2)		259 (22.6)	255 (22.3)	
Otorhinolaryngology	316 (25.9)	2340 (9.4)		248 (21.7)	212 (18.5)	
Family medicine	35 (2.9)	702 (2.8)		35 (3.1)	33 (2.9)	
Others	3 (0.3)	166 (0.7)		3 (0.3)	3 (0.3)	
Asthma medication use, mean number of prescriptions (SD) (pre-index)						
ICS	0.01 (0.15)	0.01 (0.15)	.990	0.01 (0.15)	0.01 (0.08)	.802
ICS/LABA	0.00 (0.04)	0.00 (0.08)	.585	0.00 (0.04)	0.00 (0.09)	.999
SABA	2.08 (3.77)	1.15 (3.15)	<.001	1.98 (3.77)	1.81 (4.01)	.769
Xanthine derivatives	2.83 (9.19)	1.19 (4.11)	<.001	2.99 (9.46)	1.75 (4.61)	.502
Other leukotriene modifiers	0.36 (1.41)	0.50 (1.95)	.012	0.38 (1.46)	0.38 (1.48)	.683
Oral corticosteroids	1.63 (2.75)	1.66 (2.93)	.605	1.70 (2.81)	2.00 (3.46)	.183
Injectable corticosteroids	0.23 (0.77)	0.23 (0.88)	.504	0.24 (0.79)	0.26 (0.91)	.516

BIS, budesonide inhalation suspension; ICS, inhaled corticosteroids; ICS/LABA, inhaled corticosteroids/long-acting beta-agonists; MON, montelukast; SABA, short-acting beta-agonists.

patient age could be a driver for differential asthma control outcomes, asthma control was also assessed by age group (aged 0–5 years, 6–10 years, and >10 years) in both the BIS and MON cohorts over distinct 3-month time windows, as well as cumulatively at 3, 6, 9, and 12 months post-index.

Health-care resource utilization and costs

Health-care resource utilization and costs were collected in the pre-index and post-index periods. All-cause variables were those with any ICD-10 coded office, ER, or hospital visit. Asthma-related variables were those associated with an asthma-related primary or secondary ICD-10 coded office, ER, or hospital

visit. All-cause and asthma-related costs were measured in Korean Won (₩), inflated to 2016 costs using the Consumer Price Index for Medical Goods and Services in Korea (16). Costs were sub-categorized as medical, pharmaceutical, and total costs.

Statistical analysis

Descriptive statistics and univariate statistical analyses to compare baseline variables in the pre-index period were conducted in unmatched and propensity score-matched sets. The Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables were used to determine if the baseline differences

Table 2. Adherence and persistency (matched population, post-index).

	Matched cohort		p-value
	BIS cohort (N = 1145)	MON cohort (N = 1145)	
Adherence			
Number of prescriptions, mean (SD)	4.4 (4.0)	7.2 (6.5)	<.001
Days supply per prescription (days), mean (SD)	3.5 (4.5)	7.2 (9.0)	<.001
PDC, mean %, (SD)	4.5 (6.3)	13.8 (16.3)	<.001
Persistency			
Duration of medication gaps (days), mean (SD)	39.7 (29.7)	30.1 (24.1)	<.001
Medication gap, n(%)	1062 (92.8)	1010 (88.2)	<.001
Discontinuation, n(%)	849 (74.2)	608 (53.1)	<.001
Switching, n(%)	366 (32.0)	192 (16.8)	<.001
Start/restart, n(%)	763 (66.6)	859 (75.0)	<.001
Time to first loss of persistency (days), mean (SD)	78.4 (83.4)	82.3 (79.1)	<.001

BIS, budesonide inhalation suspension; MON, montelukast; PDC, percentage of days covered.

observed across treatment cohorts were significant. Two-sided p values <0.05 denoting statistical significance were reported where applicable. All analyses were conducted using the SAS version 9.4 statistical software (Cary, NC).

Propensity score matching was performed to balance patient characteristics between the two cohorts. Propensity scores were generated from a stepwise logistic regression that modeled the odds of BIS assignment as a function of baseline characteristics such as demographics, provider characteristics, comorbidities, and other asthma-related medications and interventions. In the stepwise regression, the baseline variables statistically significant at $p < .2$ remained at each step. The greedy matching algorithm (1:N) was run to find a match from the MON cohort for each BIS patient with a final match ratio of 1:1 being selected. The quality of the match was assessed by performing descriptive statistics and univariate statistical analysis on the matched population similar to the methodology for the unmatched population described above.

Multiple variable regression modeling was performed on the unmatched and propensity score-matched population. Two models were used for the matched population (i.e., a full regression model using all baseline covariates and a reduced regression model using only the baseline covariates that were not well matched). Only results from the reduced models are presented since the results are consistent with the full regression models.

In each cohort, a negative binomial regression model comparing the number of days covered and a Cox proportional hazards model tracking time to loss of total persistency was computed, controlling for pertinent covariates. Generalized linear model log-linked cost models assuming gamma distributions were developed for asthma-related total costs, pharmaceutical costs, and medical costs adjusting for the drug cohort and other pertinent covariates.

Results

Baseline characteristics

For the overall unmatched study population, a total of 1221 patients were eligible for the BIS cohort and 24 831 were eligible for the MON cohort (Supplemental Figure E2). The average age was younger in the BIS cohort (5.4 y in BIS vs. 6.6 y in MON; $p < .001$), and the proportion of children 5 years or younger was higher in the BIS cohort (62.4% in BIS vs. 47.5% in MON; $p < .001$; Table 1). In both cohorts, medical aid patients were less than 3% ($p = 0.028$). Pediatricians were the major prescribers of both index drug therapies (49.7% in BIS and 49.9% in MON), followed by internal medicine and otorhinolaryngology specialties. Upon propensity score matching, there were 1,145 patients in both the BIS and MON cohorts. Matching was successful as indicated by the reduction of significant baseline differences between cohorts after matching (Table 1).

Adherence and persistency (matched population)

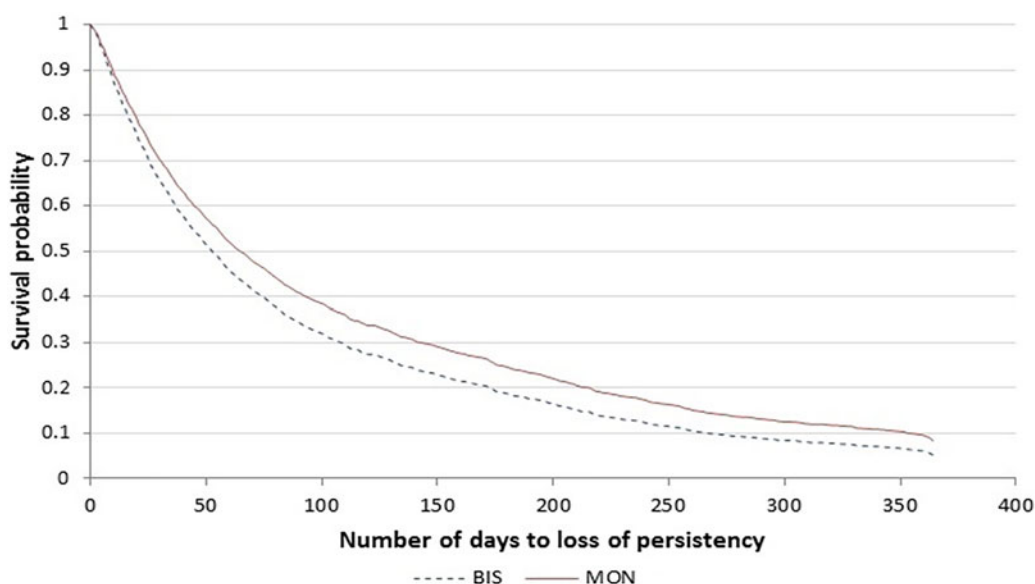
The average number of prescriptions filled in the matched population was higher in the MON cohort (Table 2). The MON cohort had a mean of 7.2 prescriptions filled compared with 4.4 prescriptions in the BIS cohort ($p < .001$). Average days' supply per prescription was also higher in the MON cohort than the BIS cohort (3.5 days in BIS and 7.2 days in MON; $p < .001$). The PDC for the MON cohort was 13.8% compared with 4.5% in the BIS cohort ($p < .001$).

There was a significant difference in persistency between the two cohorts (Table 2). The duration of medication gaps was longer in the BIS cohort than the MON cohort (39.7 days in BIS and 30.1 days in MON; $p < .001$), and the percentage of patients who experienced medication gaps was also higher in the BIS cohort (92.8% in BIS and 88.2% in MON;

Table 3. Multivariable regression (matched population, post-index).

Regression model	Regression coefficient, β (MON vs. BIS)	Coefficient interpretation (MON vs. BIS)	<i>p</i> -value
Adherence (days covered) Negative binomial model	1.077	2.936 RR	<.001
Persistency (time to the first loss of persistency) Cox proportional hazards model	−0.177	0.838 HR	<.001
All-cause total costs GLM cost model (log-linked)	0.003	0.3% Up	.912
Asthma-related total costs GLM cost model (log-linked)	0.093	9.3% Up	.007
Asthma-related medical costs GLM cost model (log-linked)	0.013	1.3% Up	.709
Asthma-related pharmaceutical costs GLM cost model (Log-linked)	0.224	22.4% Up	<.001

BIS, budesonide inhalation suspension; GLM, generalized linear model; HR, hazard ratio; MON, montelukast; RR, rate ratio.

**Figure 1.** Time to loss of persistency (matched population, post-index). BIS, budesonide inhalation suspension; MON, montelukast.

$p < .001$). Patients in the BIS cohort were more likely to experience medication discontinuation (74.2% in BIS vs. 53.1% in MON; $p < .001$) and medication switching (32.0% in BIS vs. 16.8% in MON; $p < .001$). The time to the first loss of persistency was shorter for the BIS cohort than the MON cohort (78.4 days in BIS vs. 82.3 days in MON; $p < .001$). The MON cohort, however, had a higher start/restart rate than the BIS cohort (66.6% in BIS vs. 75.0% in MON; $p < .001$).

The negative binomial regression models on the matched population showed that MON patients had a higher number of days covered after controlling for baseline characteristics ($p < .001$; Table 3). These results were affirmed by the proportional hazards modeling of the time to loss of persistency which showed that the MON cohort had a lower instantaneous rate of loss of persistency compared with the BIS cohort (hazard ratio = 0.838; $p < .001$; Figure 1, Table 3).

Asthma control (matched population)

As seen in Table 4, patients in the MON cohort tended to be less likely to experience the addition of any asthma controller agent other than BIS/MON (4.2% in BIS vs. 3.1% in MON; $p = 0.182$) or addition of BIS/MON to the index therapy (17.9% in BIS vs. 12.9% in MON). A dose escalation of the index therapy was observed in a significantly higher proportion of patients in the BIS cohort than MON (12.1% in BIS vs. 1.0% in MON; $p < .001$). However, a numerically smaller proportion of patients in the BIS cohort had more than one prescription record of a SABA canister over 100 days (0.26% in BIS vs. 0.52% in MON; $p = 0.507$).

Patients in the BIS cohort were more likely to have office visits requiring asthma control medications (nebulized SABA, an intravenous injection of a corticosteroid or a prescription for OCS within 5 days of the visit) by month 12 than the MON cohort (78.3%

Table 4. Indicators of asthma control, health-care resource utilization, and costs (matched population, post-index).

	Matched cohort		<i>p</i> -value
	BIS cohort (<i>N</i> = 1145)	MON cohort (<i>N</i> = 1145)	
Indicators of asthma control			
Medication augmentation, <i>n</i> (%)			
Addition of non-BIS/MON controller agent	48 (4.2)	36 (3.1)	.182
Addition of BIS/MON	205 (17.9)	148 (12.9)	NA
Dose escalation of index BIS/MON*	138 (12.1)	11 (1.0)	<.001
>1 recorded prescription for SABA (1 canister of 200 doses) over 100 days	3 (0.26)	6 (0.52)	.507
Exacerbation-related health-care resource utilization, <i>n</i> (%)			
Asthma-related office visit [†]	897 (78.3)	642 (56.1)	<.001
Asthma-related ER visit [†]	17 (1.5)	18 (1.6)	.865
Asthma-related inpatient hospitalization [†]	58 (5.1)	46 (4.0)	.228
Health-care resource utilization, PPPY			
All-cause, mean (SD)			
Office visits	27.9 (17.9)	28.4 (18.1)	.621
ER visits	0.3 (0.6)	0.2 (0.6)	.501
Hospitalizations			
Number of admissions	0.2 (0.5)	0.2 (0.7)	.442
LOS (days)	4.8 (4.7)	4.3 (2.2)	.545
Asthma-related, mean (SD)			
Office visits	6.6 (6.1)	8.3 (8.1)	<.001
ER visits	0.01 (0.13)	0.01 (0.09)	.217
Hospitalizations			
Number of admissions	0.03 (0.22)	0.02 (0.15)	.012
LOS (days)	6.0 (3.0)	5.7 (2.0)	.661
Costs, PPPY			
All-cause, mean (SD)			
Medical costs (₩)	606,793 (1,562,185)	570,891 (833,799)	.815
Pharmaceutical costs (₩)	167,398 (163,020)	188,028 (170,195)	<.001
Total costs (₩)	774,192 (1,621,978)	758,919 (937,721)	.259
Asthma-related, mean (SD)			
Medical costs (₩)	118,207 (228,895)	121,072 (149,528)	.054
Pharmaceutical costs (₩)	49,225 (55,687)	69,113 (73,803)	<.001
Total costs (₩)	167,432 (270,686)	190,185 (212,039)	<.001

BIS, budesonide inhalation suspension; ER, emergency room; LOS, length of stay; MON, montelukast; SABA, short-acting beta-agonists; PPPY, per patient per year; ₩, Korean won.

*Effective dose for MON is constant.

[†]With administration of nebulized SABA OR intravenous injection of a corticosteroid OR oral corticosteroid within 5 days of the visit.

vs. 56.1%, respectively; $p < .001$; Figure 2). This finding was consistent across 3, 6, 9, and 12-month time windows (Figure 2). While a numerically higher proportion of patients in the BIS cohort than the MON cohort experienced an exacerbation-related hospitalization across each of the 3-month time windows (Figure 2), this finding was not statistically significant by month 12 (5.1% vs. 4.0%; $p = 0.228$). There were no significant differences in asthma control outcomes across each of the age strata.

While post-index concomitant SABA use was high in both cohorts, it was significantly higher among BIS patients compared with MON patients (3.1 prescriptions vs. 2.0 prescriptions; $p < .001$).

Health care resource utilization (matched population)

Post-index asthma-related health care resource utilization was significantly different between the two matched cohorts. The number of post-index asthma-

related office visits was 6.6 in the BIS cohort and 8.3 in the MON cohort ($p < .001$), and the number of hospitalizations was 0.03 vs. 0.02, respectively ($p = 0.012$; Table 4).

Significant differences in post-index asthma-related costs were found between the two matched cohorts (Table 4). Post-index asthma-related total costs were lower in the BIS cohort than the MON cohort (₩ 167 432 vs. ₩ 190 185, respectively, $p < .001$), mostly driven by lower asthma-related pharmaceutical costs (₩ 49 225 in BIS vs. ₩ 69 113 in MON; $p < .001$). This may be due to a lower BIS adherence and higher MON persistency (Figure 3). Since pre-index costs were not matched, regression models estimating costs included all unmatched variables (including pre-index costs). The GLM results for the matched population showed no significant difference in the BIS versus MON cohorts for asthma-related medical costs, while the models for asthma-related pharmaceutical costs ($p < .001$) and total asthma-related costs ($p = 0.007$) were higher for the MON cohort (Table 3).

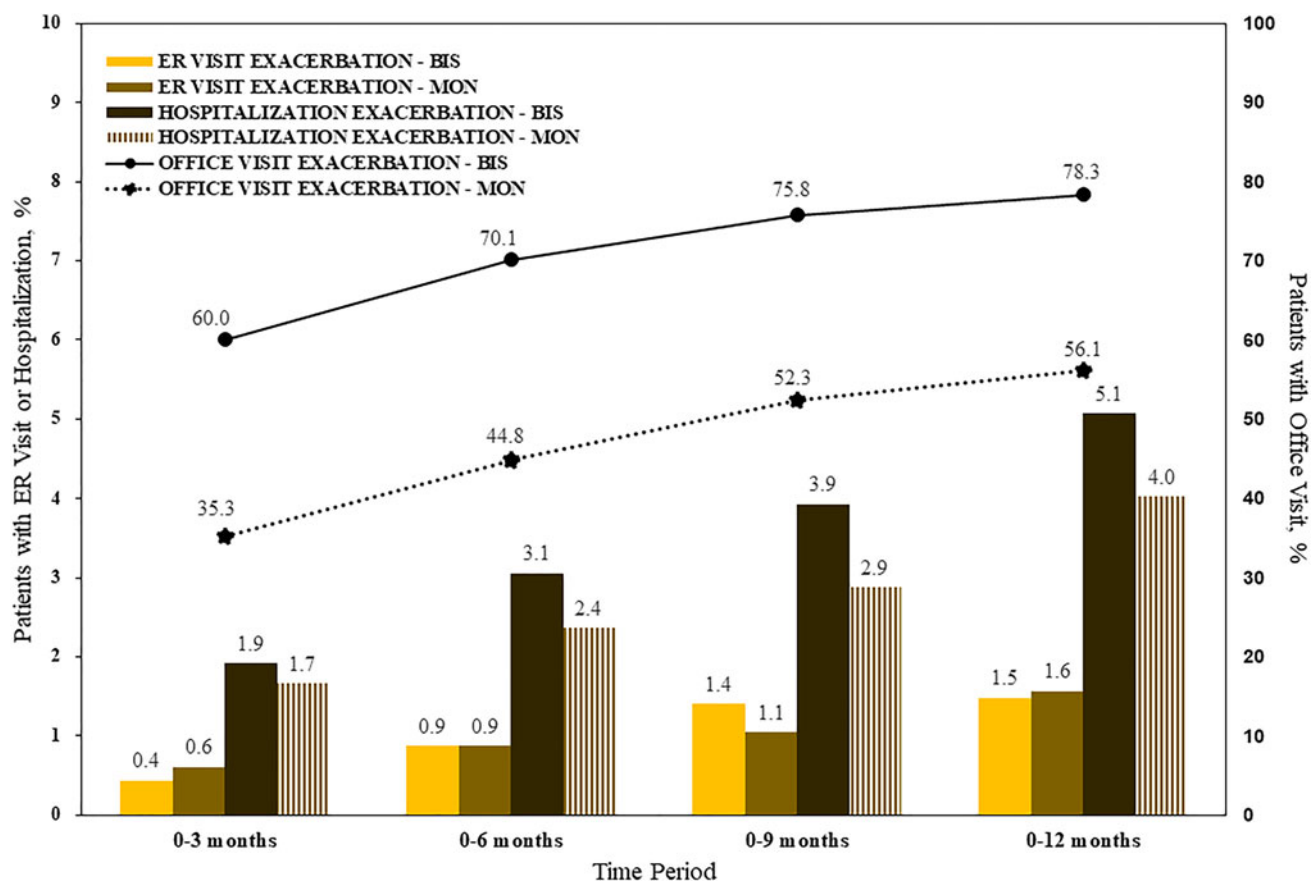


Figure 2. Outcomes of asthma control (matched population, post-index). BIS, budesonide inhalation suspension; ER, emergency room; MON, montelukast.

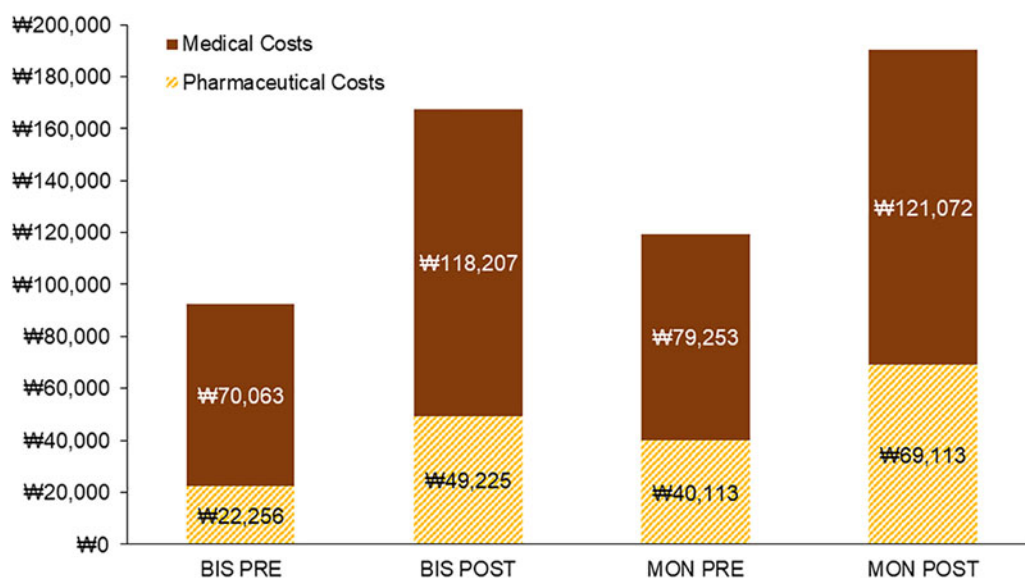


Figure 3. Asthma-related costs (Korean won, ₩; matched population, pre- and post-index). BIS, budesonide inhalation suspension; MON, montelukast.

Discussion

In the current unmatched cohort analysis, approximately 20 patients were initiated on MON for every 1 patient initiated on BIS. This finding aligns with an

evaluation of prescription patterns among pediatric allergists in Korea which indicated that MON was the most frequently prescribed controller agent for young children with mild asthma (17). The much higher

utilization of MON relative to BIS in Korea may be due to the availability of MON as an oral formulation whereas BIS has to be administered via nebulization. Physicians may prefer to prescribe MON because its oral administration could offer convenience for school-aged children. It may also reflect the reluctance of parents to expose their children to potential adverse events associated with long-term asthma-controller use. Being tall has become an important physical attribute in contemporary Korean culture and anecdotal evidence suggests that Korean parents may be averse to long-term utilization of ICS given the potential adverse effects of corticosteroids on linear growth and stature (personal communication, Dr Sung Woo Park) (18). In contrast, LTRA use does not have any effects on growth velocity (19).

In the current study, children who were initiated on MON had a significantly better medication adherence and persistency than those initiated on BIS. This finding substantiates other studies that have also found oral asthma controller medications to be associated with higher adherence and persistency rates compared with inhaled medications (20–22). However, it should be noted that the PDC was substantially low for both cohorts (13.8% for MON and 4.5% for BIS). Such low rates of medication adherence may indicate that these medications are being prescribed and/or used intermittently. Survey-based studies conducted in the Asia-Pacific region including Korea have reported an over-reliance on SABA inhalers to manage acute asthma symptoms over long-term controller agents such as ICS or LTRAs (2,5). Our study similarly showed high rates of concomitant SABA use among patients in both the BIS and MON cohorts; however, rates were significantly higher among BIS patients when compared with MON patients in the post-index period (3.1 prescriptions vs. 2.0 prescriptions; $p < .001$). Additional studies are warranted to explore physician, parent and patient perceptions associated with long-term asthma-controller medication use and their understanding of risks associated with their use.

Adherence and persistency to controller medications are well-known factors impacting asthma control (20,23). Thus, despite overall low levels of medication adherence, it is possible that the greater persistency with MON relative to BIS may contribute to better asthma control over time. Indeed, a significantly lower proportion of patients on MON had exacerbation-related office visits than BIS patients (0–12 months post-index: 56.1% vs. 78.3%; $p < .001$). A similar trend was observed for exacerbation-related hospitalizations, even though this observation did not meet statistical

significance given the low frequency of hospitalizations in both cohorts.

The current study indicates that MON patients have higher total asthma-related costs when compared with BIS patients (₩ 190 185 vs. ₩ 167 432; respectively; $p < .001$). The main driver for this finding was higher asthma-related pharmaceutical costs in MON patients than in BIS patients (₩ 69 113 vs. ₩ 49 225, respectively; $p < .001$). While the per-unit cost of BIS is higher than MON in Korea (₩ 950–1000 per BIS nebule vs. ₩ 750–1000 per MON tablet (24), respectively), MON was prescribed more frequently than BIS (7.2 prescriptions/patient vs. 4.4 prescriptions/patient; $p < .001$). Therefore, better adherence and persistency rates associated with MON relative to BIS may also drive the higher asthma-related pharmaceutical costs associated with MON, and consequently, the higher total asthma-related costs. However, additional adjusted multivariable analyses would be needed to confirm the association between adherence, persistency and asthma-related costs.

This study has limitations. The study was conducted in Korea where the use of ICS for asthma control is suboptimal and the use of SABA is excessive. Results may not be applicable to other settings where MDI ICS use is frequently used for asthma control. There may be potential misclassification bias due to errors in coding or diagnoses and procedures associated with retrospective data sources such as the HIRA database. A definitive clinical diagnosis of asthma among children is always challenging given other lower airway respiratory conditions that may have common overlapping symptoms in children (25,26). Consequently, it is possible that children that presented with lower respiratory airway complaints (such as cough-variant asthma or bronchiolitis) may have been misdiagnosed as bronchial asthma and coded as such. Misclassification associated with more aggressive coding strategies to increase reimbursement by reporting providers and institutions is also possible.

Bias may have been introduced into the estimation of PDC because of inconsistency in recording days of supply for BIS nebulizers. There may also be an omitted variable bias and residual confounding associated with this study, given that pertinent clinical findings such as symptoms, lab results, or spirometry assessment data were not available for analysis. Exacerbation and asthma control measures that were utilized in this study were based on algorithms of readily available data and, thus, may have had limited applicability since other “true” exacerbation events defined by lung function or symptoms (e.g., nocturnal awakenings,

wheezing, shortness of breath, etc.) were not captured. Finally, there are high rates of reported concomitant use of “over the counter” traditional medicines in Korea that may have either positively or negatively impacted asthma control. These data were not captured in this data source.

Despite these limitations, very few studies have explored “real-world” asthma outcomes associated with mild pediatric asthma in Korea. This study is the first to systematically explore medication utilization, treatment persistency, health-care resource use, costs, and asthma control outcomes associated with two asthma controller agents, BIS and MON, among Korean children with mild asthma in the “real-world” setting. A major strength of this study is that findings are generalizable to the entire Korean population, given that claims from over 90% of the Korean population are captured by the HIRA database.

Conclusions

Montelukast patients had better adherence and longer time to loss of persistency when compared with BIS patients. Montelukast patients were also less likely to experience an exacerbation-related office visit in the post-index period than BIS patients. While MON patients had higher asthma-related total costs compared with BIS patients, these costs may be driven by higher pharmaceutical costs due to prescribing practices and better treatment adherence/persistency associated with MON.

Acknowledgements

Editorial assistance was provided by Erin P. Scott, PhD, of Scott Medical Communications. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA. The study sponsor participated in the design of the study, interpretation of the data, and writing of the manuscript. The first draft of the manuscript was written by Jina Shin, PharmD and S.H. Hong, PhD. All authors contributed to the writing of the manuscript and approved the manuscript for submission.

Declaration of interests

JS, SJO, SWP, and SHH have nothing to disclose. TP, KT, and EU are employees of Merck & Co., Inc., Kenilworth, NJ. PN and HF are paid consultants for Merck.

Funding

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA.

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Supplemental Figure Legends

Supplemental Figure E1. Study schema.

Supplemental Figure E2. Patient selection. BIS, budesonide inhalation suspension; ER, emergency room; GINA, Global Initiative for Asthma; ICD-10 CM, International Classification of Diseases, 10th revision, Clinical Modification; MON, montelukast.

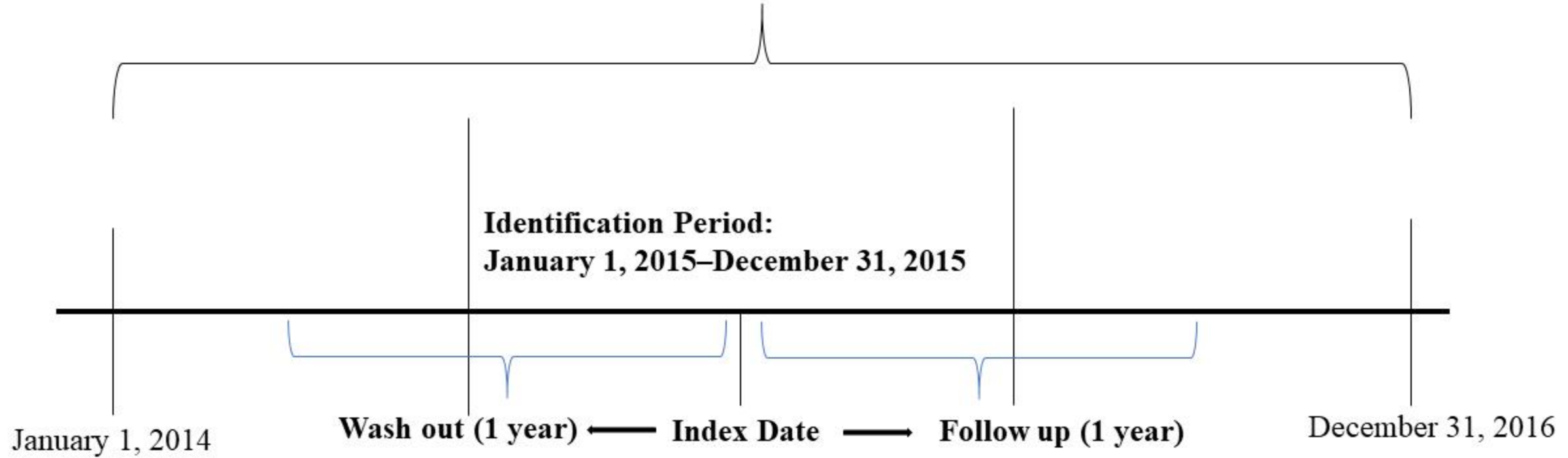
Observation Period: January 1, 2014–December 31, 2016

**Identification Period:
January 1, 2015–December 31, 2015**

January 1, 2014

Wash out (1 year) ← Index Date → Follow up (1 year)

December 31, 2016



Aged 2 through 17 years during identification period

N=1,025,672

Patients with medical records of the following during the identification period:

- At least two distinct days with record of an office visit separated by at least 7 days with a primary or secondary ICD-10 CM diagnosis of asthma (J45.XX)
- An ER visit with a primary or secondary ICD-10 CM diagnosis of asthma
- An inpatient hospital stay with a primary or secondary admission ICD-10 CM diagnosis of asthma

N=496,450

BIS Cohort

Have at least two prescription records of low dose BIS with a primary diagnosis of asthma during the study time frame

N=3,187

Have data captured for a period of 1 year before and 1 year after the index date

N=3,187

Excluded patients fall under GINA therapy category 3 through 5 during the pre-index period and including the index date

N=1,891

Excluded patients have used any controller medications in the 30 day pre-index window prior to the index date including low dose BIS or MON

N=1,221

MON Cohort

Have at least two prescription records of MON associated with a primary diagnosis of asthma during the study time frame

N=84,599

Have data captured for a period of 1 year before and 1 year after the index date

N=84,599

Excluded patients fall under GINA therapy category 3 through 5 during the pre-index period and including the index date

N=43,847

Excluded patients have used any controller medications in the 30 day pre-index window prior to the index date including low dose BIS or MON

N=24,831