Original article

Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma

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Background: Limited evidence exists on adherence and effectiveness of combination therapy (inhaled corticosteroids and long-acting β_2-agonists in the same inhaler) in asthma.
Objective: To compare persistence, adherence, and effectiveness between patients with asthma 16 to 44 years old starting combination or concurrent therapies (inhaled corticosteroids and long-acting β_2-agonists in 2 different inhalers).
Methods: This retrospective 1-to-1 matched cohort included newly treated asthmatics with either a combination or concurrent therapy selected from the Régie de l'assurance maladie du Québec database between 1999 and 2002. Persistence was determined by Kaplan-Meier and Cox regression analyses. Adherence was estimated by the number of prescriptions filled during the first year and compared between the 2 drug regimens using a linear regression model. Treatment effectiveness to reduce the rate of moderate to severe asthma exacerbations was estimated with Poisson regression models.
Results: Persistence fell to 10% and 5% after 12 months for combination and concurrent users, respectively. Combination users were found to be 17% less likely to stop their treatment (adjusted hazard ratio, 0.83; 95% CI, 0.78, 0.88) and filled on average 0.9 more prescription per year than concurrent users ($P = .0001$). Combination users were also found to be 17% less likely to have a moderate to severe asthma exacerbation (adjusted rate ratio, 0.83; 95% CI, 0.75, 0.91).
Conclusion: The observed differences in treatment persistence and adherence were found to be associated with a reduction in the rate of moderate to severe asthma exacerbations among combination users.
Clinical implications: Combination therapy might be preferred to concurrent therapy for patients with asthma with low adherence to controller therapies. (J Allergy Clin Immunol 2006;118:574-81.)

Key words: *Asthma, combination therapy, concurrent therapy, persistence, adherence, effectiveness*

The international guidelines (Global Initiative for Asthma)[1] and the latest Canadian Asthma Consensus[2] guidelines uphold the concept of asthma management as a continuum, contingent on underlying symptoms, severity, and pulmonary tests results. When asthma is not optimally controlled with inhaled corticosteroids (ICSs) alone, the addition of long-acting β_2-agonists (LABAs) to ICSs is accepted as the most effective therapy to control moderate to severe asthma.[3] This therapeutic approach is also supported by National Asthma Education and Prevention Program guidelines.[4]

Inhaled corticosteroids and LABAs have a complementary effect,[5-8] treating underlying airway inflammation and obstruction, respectively.[3,9,10] It has been shown that this regimen provides greater control than increasing the dose of ICSs[11,12] and may also improve outcomes (lung function, exacerbation rates, and quality of life) in patients with asthma who remain symptomatic on ICSs.[13]

Concurrent or combined administration of ICSs and LABAs may not be equivalent. *Concurrent* entails the manipulation of 2 different inhalers (1 for each drug), whereas *combination* involves a single inhaler (containing both agents).[14] Moreover, evidence suggests that ICSs and LABAs in a single inhaler may be superior in reducing asthma exacerbations than the administration of the same products in 2 separate inhalers.[15]

Furthermore, adherence to asthma treatments declines as the regimen becomes more complicated by increasing the number of medications and/or the number of daily doses.[16,17] Consequently, it has been hypothesized[18,19] that the use of combination inhalers can improve patients' adherence, which may lead to overall asthma control.[20-22] Two published studies[23,24] so far have reported improved adherence with combination therapy in clinical practice, but to our knowledge, no study reported the effect of this improved adherence on clinical outcomes in real clinical practice.

Therefore, we performed a cohort study to compare treatment persistence and adherence as well as treatment

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Abbreviations used
ED: Emergency department
ICD-9: International Classification of Disease, 9th revision
ICS: Inhaled corticosteroids
LABA: Long-acting β_2-agonists
RAMQ: Régie de l'assurance maladie du Québec

effectiveness between patients with asthma starting a combination or a concurrent therapy.

METHODS

Sources of data

This study required access to claims data from the Régie de l'assurance maladie du Québec (RAMQ) and MED-ECHO databases. The RAMQ databases contain administrative data files on residents covered by the provincial health care and by the public drug insurance plans, including approximately 43% of the total population of the province of Quebec, Canada.[25] The RAMQ Demographic file lists age, sex, postal code, and year of death. The RAMQ Medical Services file includes claims data on medical services such as site of medical practice (outpatient clinic, emergency department [ED], hospitalization); nature of the medical act, date, and diagnostic information (International Classification of Disease, 9th revision [ICD-9] codes); and the encrypted identification and physician's specialty.[26] The RAMQ Prescription Drugs file, which has been validated for research and previously used for pharmacoepidemiologic research studies,[27,28] contains data on prescriptions filled at community pharmacies: drug name, date, dose, quantity, and duration as indicated by the pharmacist, as well as the encrypted identification and prescribing physician's specialty. The MED-ECHO database contains data on acute care hospitalizations, such as date of admission, length of stay, and primary and secondary diagnoses. All of these files also contain the individual's health insurance number, which is the link between them.

Study population

A cohort of 12,386 patients was identified from the RAMQ database between January 1, 1999, and September 30, 2002. At the time of inclusion in the cohort—which corresponded to the date of the beginning of a combination or a concurrent therapy—subjects were required to be (1) between 16 and 44 years old inclusively, (2) insured under the Quebec drug plan in the preceding year and at least 30 days after cohort entry, and (3) exempt of any recorded prescription for a combination or a concurrent ICS and LABA therapy in the preceding year. For each patient included in the cohort, we obtained from RAMQ sociodemographic data, physician characteristics, and data on all prescriptions filled and medical services dispensed between January 1, 1998, and December 31, 2002. We also obtained from MED-ECHO data on all acute care hospitalizations during the same period.

From the 12,386 individuals who met the eligibility criteria, the final 1-to-1 combination to concurrent matched cohort was formed (n = 5118) on the basis of (1) markers of asthma severity: number of prescriptions of ICS filled in the year preceding cohort entry and daily dose of ICS prescribed at cohort entry (ie, first prescription of the combination or concurrent therapy), and (2) markers of asthma control: number of prescriptions of oral corticosteroids and short-acting β_2-agonists filled in the year before cohort entry. Subjects were followed from the date of the first prescription of a combination or a concurrent therapy (cohort entry, corresponding to the initiation of the therapy) until the earliest of these events: December 31, 2002; death; a switch between a concurrent and a combination therapy; or loss of coverage under the drug insurance plan.

Combination and concurrent therapy

The concurrent therapy was reconstructed by using an algorithm based on the dispensing date, amount dispensed, duration of treatment, and the name of the medication. Patients considered in the concurrent group had refilled prescriptions of ICS (fluticasone, budesonide, beclomethasone) and LABA (salmeterol, formoterol) within an interval of 15 days between the dispensing dates. Patients considered in the combination group were simply identified if they had 1 filled prescription for that treatment (fluticasone propionate/salmeterol or budesonide/formoterol) because a single inhaling device combines both agents.

Treatment persistence and adherence

Assessing failure to refill prescriptions constitutes a reliable and objective measure of persistence in large patient groups.[29] The primary outcome of persistence was defined as having prescriptions of the ongoing therapy continuously renewed within a prespecified grace period defined as the sum of 3 times the duration of the current prescription (in days) plus all overlaps accumulated since the beginning of the therapy. An overlap was considered when a patient refilled a prescription before its end. The discontinuation date was the last day of drug supply—that is, the end date of the last filled prescription plus all overlaps. For concurrent patients, a discontinuation was observed if they ceased either or both LABA or ICS prescriptions.

Treatment adherence was defined as the number of prescriptions of either a combination or a concurrent therapy filled during the first year of treatment. This measure of adherence was calculated among patients who had at least 1 year of follow-up.

Treatment effectiveness and outcomes

Treatment effectiveness was assessed by comparing the rate of moderate to severe asthma exacerbations occurring during the first year of treatment between users of combination and concurrent therapies. Exacerbations were defined as a filled prescription of an oral corticosteroids, or a visit to an ED or a hospitalization for asthma (ICD-9 code 493) recorded in the RAMQ or MED-ECHO databases. Markers of asthma exacerbation occurring within 15 days were counted as only 1 exacerbation. As a secondary outcome, we also compared the weekly number of doses of short-acting inhaled β_2-agonists.

Covariables

Potential confounding variables and determinants of persistence and adherence included age (5-year differential), sex (male vs female), receipt of social assistance (yes/no), area of residency (urban versus rural), and the number of different medication prescription filled in the year before cohort entry. Markers of asthma severity and control were also considered: prescribed daily dose of ICS ($\leq$250, >250-500, and >500 μg fluticasone or equivalent) at treatment initiation, number of prescriptions filled in the year preceding cohort entry for ICS, oral corticosteroids, and short-acting β_2-agonists; hospitalization for asthma (yes/no); visit to an ED for asthma (yes/no); and medical visits to a respiratory physician for asthma (yes/no) in the year before cohort entry. We also considered the specialty of the physician who prescribed the initial therapy (general practitioner, respiratory physician, or other specialist) as well as records for at least 1 prescription of antileukotrienes (yes/no) or theophylline (yes/no) in the year before cohort entry.

Statistical analysis

Patients' characteristics including sociodemographics, use of prescribed medications, and use of health care services for asthma

TABLE I. Patient characteristics for new users of a combination or a concurrent therapy

	Combination (n = 2559)	Concurrent (n = 2559)
Sociodemographic characteristics		
Age (y), mean ± SD	32.5 ± 8.2	32.7 ± 8.2
Sex (% men)	38.4	35.0
Receipt of social assistance (%)	41.5	47.3
Living in a rural area (%)	21.8	24.0
Different medications (n)	6.5 ± 5.6	6.7 ± 5.9
Initial prescription of combination or concurrent therapy		
Prescribed daily dose of ICS (μg), mean ± SD*†	761.4 ± 363.7	858.7 ± 467.2
Users (%)		
≥250	4.3	
>250-500	33.8	
>500	61.8	
Prescribing physician (%)		
Family physician	87.1	74.4
Respiratory physician	7.8	18.9
Other specialists	5.1	6.6
Use of health care services in the year preceding cohort entry		
≥1 ED visit for asthma (%)	11.1	15.3
≥1 Hospitalization for asthma (%)	2.1	4.3
≥1 Visit to a respiratory physician for asthma (%)	7.7	16.2
Visits to a family physician per patient (n), mean ± SD	6.7 ± 7.9	7.2 ± 8.2
Visits to a family physician for asthma per patient (n), mean ± SD	0.8 ± 1.3	1.0 ± 1.7
Prescriptions filled in the year preceding cohort entry		
Prescriptions/patient (n), mean ± SD		
ICS†	1.4 ± 2.2	
Short-acting β_2-agonists†	2.7 ± 4.0	
Oral corticosteroids†	0.3 ± 0.8	
Theophylline, users (%)	1.8	3.2
Antileukotriene, users (%)	5.0	4.5

NA, Not applicable because in the combination therapy, ICSs and LABAs are included in a single inhaler.
*Daily dose calculated on the basis of fluticasone equivalent.
†The distribution of these variables is identical in both groups because patients were matched on these variables.

were compared between users of combination and concurrent therapies. Treatment persistence between the 2 drug regimens was compared by using 3 analyses. First, we compared the proportion of patients without prescription refill during the year after the initiation of therapy with a χ^2 test. This analysis was restricted to patients who had at least 1 year of follow-up. Second, the cumulative persistence rate was estimated by using the Kaplan-Meier failure time analysis[30] and compared between regimens by using a log-rank test.[31] For patients using the concurrent therapy, we also estimated Kaplan-Meier curves for ICS and LABA separately and compared them with a log-rank test. We also performed a sensitivity analysis to test the effect of the predefined grace period by re-estimating persistence using grace periods defined as 2 and 4 times the duration of the latest prescription plus overlaps. Third, a Cox regression model was used to compare further the probability of nonpersistence between both drug regimens while adjusting for all covariables described. After that, treatment adherence was first crudely compared between users of combination and concurrent therapies with the average number of prescriptions filled during the year after treatment initiation. We also estimated the adjusted mean difference in the number of filled prescriptions between combination and concurrent users using a linear regression model, allowing adjustment for all covariables described.

Finally, we assessed the relative effectiveness of the 2 drug regimens to control asthma and reduce the rate of moderate to severe exacerbations. We first described the rate of use of oral corticosteroids and short-acting inhaled β_2-agonists and of ED visits and hospitalizations for asthma during the period of treatment persistence and in the 6-month period after treatment cessation. We then used 2 Poisson regression models to compare further the rate of moderate to severe asthma exacerbations between combination and concurrent therapies, while adjusting for confounding variables. One model covered the period in which patients were persistent to their tratment, and the other model covered the year after treatment initiation. Similarly, we compared the weekly number of doses of short-acting inhaled β_2-agonists using 2 linear regression models. The final models were found by using a backward selection strategy.

RESULTS

The final matched cohort consisted of 5118 patients: 2559 new users of combination therapy 1-to-1 mathched to 2559 new users of concurrent therapy. During the study follow-up among combination users, 2 patients died (0.08%), 11 switched to the concurrent therapy (0.4%), and 223 stopped being covered by the RAMQ drug plan (8.7%). The corresponding values were 3 (0.12%), 29 (1.1%), and 55 (2.1%) in the concurrent group. Table I presents patients' characteristics. Sociodemographic variables were quite comparable between the 2 drug regimens,

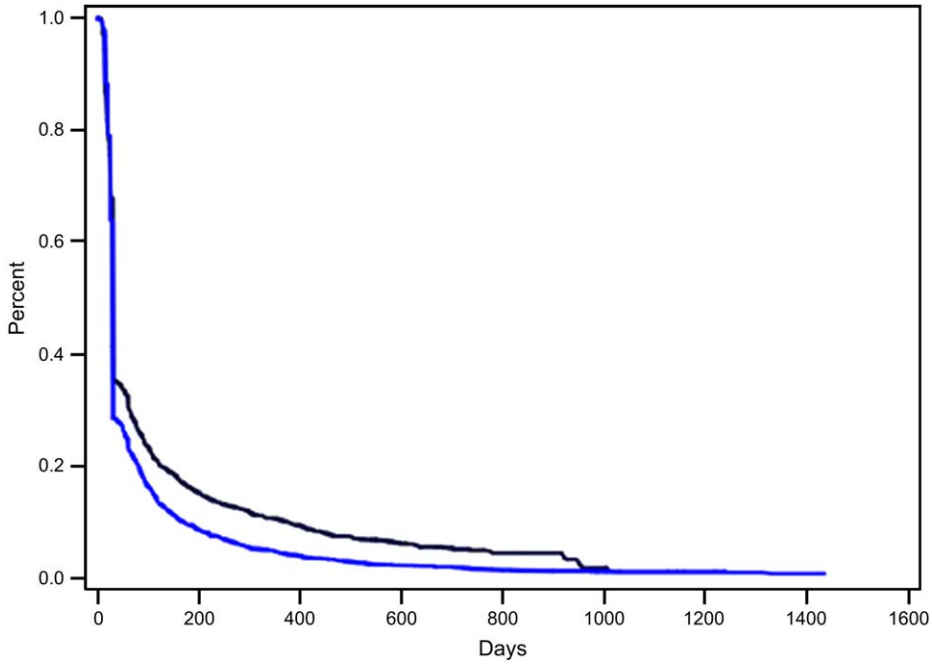

FIG 1. Kaplan-Meier curves comparing persistence over time between both study groups. Grace period of 3 times the duration of the latest prescription plus overlaps. *Black,* New users combination therapy; *blue,* new users concurrent therapy.

whereas despite matching, new users of concurrent therapy appeared to have more severe asthma before treatment initiation than new users of combination therapy because they had higher doses of ICSs prescribed at cohort entry on average, were more often treated by a respiratory physician, and had more ED visits and hospitalizations for asthma.

Treatment persistence and adherence

We estimated that 44.2% and 51.5% of the patients who started a combination and concurrent therapy, respectively, did not renew their initial prescription during the first year ($P = .0001$). Fig 1 presents the Kaplan-Meier curves representing the cumulative percentages of patients persisting on therapy at different points in time comparing combination (n = 2559) and concurrent (n = 2559) users. The graph shows that combination users tended to be more persistent on treatment than concurrent users (*P* value for log-rank test < .0001). We found that 10% of combination users were still persistent 1 year after the initiation of therapy, whereas this percentage was slightly below 5% for concurrent users. The corresponding figures at 2 years for each regimen were 5% and below 2%, respectively. The sensitivity analyses based on 2 and 4 times the duration of the latest prescription plus overlaps showed that regardless of the grace period definition, patients on combination therapy were found to be slightly more persistent than patients on concurrent therapy (*P* value for log-rank test < .0001 for both grace periods).

We also looked at the persistence on LABAs and ICSs separately among concurrent therapy users. This analysis showed a slightly better persistence rate for ICSs compared with LABAs (*P* value for log-rank test < .0001). One year after the initiation of the concurrent therapy, approximately 11% of the patients were still using their LABAs, and 13% were still using their ICSs. These values were close to 5% for both agents after 2 years (for a Kaplan-Meier graph, see Fig E1 in the Online Repository at www.jacionline.org).

Table II lists the crude and adjusted hazard ratios for discontinuation as determined by the Cox regression model. After adjusting for all potential determinants of discontinuation, we found that combination users were 17% less likely to discontinue their treatment (rate ratio, 0.83; 95% CI, 0.78, 0.88) than concurrent users. This model also showed that older patients, men, patients receiving social assistance, and patients taking a greater number of different medications were significantly less likely to discontinue their treatment. We found that patients with markers of asthma severity and lack of control were significantly less likely to discontinue their treatment. On the other hand, patients who received more than 500 mcg ICSs in fluticasone equivalent at treatment initiation were found to be more likely to discontinue than patients receiving lower doses.

In terms of adherence, we found that combination and concurrent users filled on average 3.5 (SD, 3.4) and 2.7 (SD, 2.6) prescriptions during the first year after treatment initiation, respectively. Adherence was calculated among the 1369 combination users and 1739 concurrent users who had at least 1 year of follow-up. We also observed that concurrent users filled approximately the same number of

TABLE II. Crude and adjusted hazard ratios of treatment discontinuation comparing new users of combination (n = 2559) and concurrent therapy (n = 2559)

	Crude HR (95% CI)	Adjusted HR* (95% CI)
Combination versus concurrent therapy	0.83 (0.79-0.88)	0.83 (0.78-0.88)
Sociodemographic characteristics		
Age (5 y difference)	0.96 (0.95-0.98)	0.96 (0.94-0.97)
Male vs female	0.90 (0.85-0.95)	0.92 (0.86-0.98)
Social assistance (yes/no)	0.84 (0.79-0.89)	0.87 (0.82-0.93)
Living in rural vs urban area	0.98 (0.91-1.04)	0.94 (0.87-1.00)
Initial prescription of combination or concurrent therapy		
Daily dose of inhaled corticosteroid (fluticasone equivalent) prescribed (μg)		
≤250	Reference	Reference
>250-500	0.85 (0.74-0.98)	1.00 (0.87-1.16)
>500	1.34 (1.16-1.54)	1.60 (1.39-1.84)
Specialty of the prescribing physician		
General practitioner	Reference	Reference
Respiratory physician	0.78 (0.72-0.86)	0.78 (0.70-0.86)
Other specialist	0.92 (0.83-1.03)	0.87 (0.78-0.97)
Prescriptions filled in the year preceding cohort entry		
ICSs (each additional prescription)	0.85 (0.84-0.87)	0.90 (0.89-0.92)
Corticosteroids (each additional prescription)	0.96 (0.92-0.99)	1.00 (0.97-1.04)
Short-acting β_2-agonists (each additional prescription)	0.92 (0.91-0.93)	0.96 (0.95-0.96)
Antileukotriene (yes/no)	0.71 (0.62-0.82)	0.85 (0.73-0.98)
Theophylline (yes/no)	0.71 (0.59-0.85)	0.98 (0.81-1.18)
Number of different medications (each additional prescription)	0.976 (0.97-0.981)	0.993 (0.987-0.999)
Health care services for asthma in the year before cohort entry (yes/no)		
Hospitalization	0.94 (0.80-1.11)	1.06 (0.88-1.27)
Visit to an ED	0.82 (0.76-0.89)	0.85 (0.77-0.93)
Medical visit to a respiratory physician	0.85 (0.78-0.93)	0.95 (0.86-1.06)

*Hazard ratios (HRs) adjusted for all variables included in the table.

prescriptions for ICSs (3.4; SD, 3.2) and LABAs (3.5; SD, 3.1). The linear regression model including all covariables confirmed the crude result, with an adjusted mean difference in treatment adherence of 0.9 filled prescription per year, on average, between combination and concurrent users ($P = .0001$).

Treatment effectiveness

Tables III and IV present the results of the effectiveness analyses. On the basis of crude rates presented in Table III, we can see that concurrent users had significantly more exacerbations and used more short-acting inhaled β_2-agonists than combination users during the tratment period and after the treatment was stopped. We can also see from Table III that the rate of exacerbations and the use of short-acting inhaled β_2-agonists was much lower after the treatments were stopped than during the treatment period—that is, when patients where still persistent to their therapy. From the results presented in Table IV, we observe that the adjusted rate of moderate to severe asthma exacerbations during the treatment period was similar among combination and concurrent users (adjusted rate ratio, 1.00; 95% CI, 0.88, 1.13). On the other hand, when the period of observation was the first year after treatment initiation (regardless of when the treatment was stopped), we found that combination users were 17% less likely to have an exacerbation than concurrent users (adjusted rate ratio, 0.83; 95% CI, 0.75, 0.91). We also found that patients with combination therapy used less short-acting inhaled β_2-agonists (average difference of −0.35 dose per week; 95% CI, −0.55, −0.15).

DISCUSSION

Patients on a combination therapy were found to be more persistent and adherent than patients treated with ICSs and LABAs taken in 2 different inhalers. Persistence with combination and concurrent therapies fell to 10% and 5%, respectively, 12 months after initiation, and overall, combination users were found to be 17% less likely to stop their treatment than concurrent users. Adherence was also found to be low for both regimens: users of combination and concurrent therapy filled on average 3.5 and 2.7 prescriptions during the first year of treatment.

These differences in treatment persistence and adherence resulted in a difference in treatment effectiveness. When an intent-to-treat approach was used to compare treatment effectiveness during the first year after initiation, we found that combination users were 17% less likely to have moderate to severe asthma exacerbations than concurrent users. This result could result from increased efficacy of the combination, increased adherence to the combination, or both. Because the 2 drug regimens were

TABLE III. Crude rate of moderate to severe asthma exacerbations and use of short-acting inhaled β_2-agonists

	During treatment			6 mo after treatment cessation		
	Combination	Concurrent	*P* value	Combination	Concurrent	*P* value
Number of patients	2559	2559		2559	2559	
Moderate to severe asthma exacerbations (rate per patient per year)	0.7	1.1	<.0001	0.2	0.4	<.0001
Oral corticosteroids	0.8	1.3	<.0001	0.2	0.4	.001
ED visit for asthma	0.2	0.4	<.0001	0.1	0.2	.054
Hospitalization for asthma	0.01	0.03	.078	0.01	0.01	.620
Mean number of doses per week of short-acting inhaled β_2-agonists ± SD	5.7 ± 8.6	7.0 ± 9.3	<.0001	1.8 ± 3.8	2.5 ± 4.4	<.0001

TABLE IV. Crude and adjusted rate ratio of moderate to severe asthma exacerbations* comparing combination and concurrent therapy

	Combination versus concurrent			
Moderate to severe asthma exacerbations*	**Crude rate ratio**	**95% CI**	**Adjusted rate ratio**	**95% CI**
During treatment persistence	0.88	0.78, 0.99	1.00†	0.88, 1.13
During the year following treatment initiation	0.74	0.67, 0.81	0.83‡	0.75, 0.91
Weekly number of short-acting inhaled β_2-agonists	**Crude mean difference**	**95% CI**	**Adjusted mean difference**	**95% CI**
During treatment persistence	−1.33	−1.83, −0.84	−1.05§	−1.53, −0.58
During the year following treatment initiation	−0.41	−0.65, −0.16	−0.35‖	−0.55, −0.15

*Moderate to severe asthma exacerbations are defined as a filled prescription of an oral corticosteroids, a visit to an ED, or a hospitalization for asthma (ICD-9 code 493) recorded in the RAMQ or MED-ECHO databases.
†During treatment persistence: rate ratio adjusted for the receipt of social assistance, daily dose of ICSs prescribed at treatment initiation (cohort entry), specialty of prescribing physician at treatment initiation, total number of different medications dispensed, hospitalization for asthma, visit to an ED for asthma, visit to a respiratory physician, and use of oral corticosteroids, antileukotrienes, and short-acting inhaled β_2-agonists in the year preceding treatment initiation.
‡During the year after treatment initiation: rate ratio adjusted for the receipt of social assistance, daily dose of ICSs prescribed at treatment initiation (cohort entry), specialty of prescribing physician at treatment initiation, total number of different medications dispensed, hospitalization for asthma, visit to an ED for asthma, and use of oral corticosteroids and short-acting inhaled β_2-agonists in the year preceding treatment initiation.
§During treatment persistence: mean difference adjusted for the receipt of social assistance, daily dose of ICSs prescribed at treatment initiation (cohort entry), specialty of prescribing physician at treatment initiation, and use of antileukotrienes and short-acting inhaled β_2-agonists in the year preceding treatment initiation.
‖During the year after treatment initiation: mean difference adjusted for the receipt of social assistance, ED visit for asthma, and use of antileukotrienes and short-acting inhaled β_2-agonists in the year preceding treatment initiation.

found to have comparable effectiveness when patients were still under treatment and increased adherence for the combination was documented, the data support increased adherence as the most important mechanism of the increased effectiveness of combination versus concurrent therapy observed in the current study. To our knowledge, our study is the first to report a relative increase in effectiveness for combination therapy as compared with concurrent therapy. This result is also consistent with a meta-analysis performed on the relative efficacy of fluticasone and salmeterol provided as a combination versus a concurrent therapy, reporting an average increase of 5.4 L/min in the change from baseline in the morning peak expiratory flow in favor of the combination therapy.[9] However, in this meta-analysis study based on a 12-week follow-up period, the authors did not discuss treatment adherence and how it might have contributed to the observed increased efficacy in favor of the combination therapy.

Our findings on treatment adherence are consistent with those of 2 retrospective cohort studies that measured treatment adherence using the number of prescriptions recorded in a United States claims database over a 12-month period.[23,24] Stoloff et al[23] observed that patients who were prescribed a LABA/ICS combination obtained significantly more refills (4.06) compared with patients prescribed fluticasone and salmeterol concurrently (2.35). Similar results were observed in the other study. One major methodologic difference between these studies and ours is that their patients were not newly treated with a combination or a concurrent therapy at the beginning of the study. In these studies, patients on concurrent therapy might have been treated for a longer period than patients on combination therapy at the beginning of the 12-month observation period, because LABAs arrived on the market a few years before the combination therapy. As we observed in our study, persistence tends to decrease over time, and this phenomenon might explain why the difference in adherence observed in our study is smaller than the difference observed in these studies.

One phenomenon that might explain this high rate of treatment cessation is the patient's lack of perceived need for the medication over time. The analysis we performed on asthma outcomes (filled prescriptions of oral corticosteroids, high doses of short-acting inhaled β_2-agonists, ED visits and hospitalizations for asthma) occurring in the 6-month period after treatment cessation clearly showed us that asthma control was already improved compared with when the combination or concurrent therapy was initiated. This might have contributed to encourage patients to stop their medication, thinking that their disease was under control. This hypothesis is also supported by the results found in the Cox regression model showing that patients without markers of uncontrolled and severe asthma were found to be more likely to stop their treatment. One frequent argument in favor of combination therapy instead of ICSs and LABAs in separate inhalers is that patients might be more likely to stop their ICSs and continue their LABAs, because they might perceive more easily the benefit of the LABAs. However, in our study, we found that patients who started a concurrent therapy were slightly more likely to stop LABAs than ICSs.

Although using 1 inhaler instead of 2 could likely be easier to manage for patients, it is worthy, as in any observational study, to review the biases that might have distorted the magnitude of our results. Disease severity and degree of asthma control before treatment initiation could affect persistence, adherence, and effectiveness. One may speculate that sicker patients might be more likely to perceive a benefit from their asthma preventive therapy and thus be more likely to be persistent. Consequently and with respect to our study, all efforts were made to control differences between treatment groups by matching patients on well known markers of disease severity and control (short-acting β_2-agonists, ICS and oral corticosteroid use in the year before cohort entry, and on the prescribed dose of ICS at treatment initiation).[32-34] To adjust for any remaining differences even after matching, we performed regression analyses including several potential confounders, such as ED visits and hospitalizations for asthma. Despite matching and adjustment for potential confounders in the regression models, we cannot completely rule out the possibility of residual confounding, because patients in the concurrent group appeared to have a higher level of severity and lack of control on the basis of higher frequency of ED visits and hospitalizations for asthma before cohort entry. However, the fact that the 2 drug regimens were found to have comparable effectiveness when patients were persistent to therapy, despite the fact that concurrent users appeared to have more severe and uncontrolled asthma before treatment initiation, provides evidence of the capacity of our model to adjust for pretreatment asthma severity and control. One weakness of this study is thus the absence of clinical measures of asthma severity and control, such as pulmonary function tests and symptoms scores.

Another weakness of our study is the fact that dispensed medications might not coincide exactly with the actual intake of the medications, potentially resulting in drug use misclassification.[35] Moreover, the asthma diagnosis was not confirmed with pulmonary function. Because a LABA/ICS regimen could also likely be prescribed to treat other conditions, such as chronic obstructive pulmonary disease, patients were included in our study only if they were less than 45 years old at cohort entry, thereby lessening the likelihood of including patients with chronic obstructive pulmonary disease.

The main strength of this study is that the analyses were performed on a large administrative database and thus represent the real-life use of these drugs in clinical practice, with a large sample size providing high statistical power to the analyses. The use of an administrative database to measure drug exposure also eliminates the potential of recall bias.[35] Moreover, our sensibility analyses results showed that the Kaplan-Meier estimators were not influenced by the duration of the selected grace period for treatment renewal; differences of similar magnitude in the persistence rate could still be observed between groups, regardless of the grace period.

Our results demonstrate that persistence and adherence to LABA/ICS controller therapies currently used in the prophylaxis of asthma remain very poor among adult patients with asthma, with many patients taking their medication sporadically. Despite low treatment persistence and adherence, the observed difference in favor of the combination therapy was found to be associated with an increase in drug effectiveness to reduce the rate of moderate to severe asthma exacerbations. On the basis of these results, we should question the effect of treatment nonadherence on a patient's health, as well as on the use and cost of health care services.

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