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Original article

Patient response to the management during the acute presentation of cough variant Asthma: Retrospective cohort study

Samir Ibrahim Arif [a], Yasser S. Amer [b,c], Turki Adnan Alkamal [d], Mohammad Abdulrahman Binsaeed [e], Bandar Ibrahim Arif [f], Meshari Dhaifallah Albaqami [g], Ousama Bakri Alfahed [a]

[a] Family Medicine Center, King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia
[b] CPG and Quality Research Unit, Quality Management Department, Pediatrics Department, King Saud University Medical City, Riyadh, Saudi Arabia
[c] Research Chair for Evidence-Based Health Care and Knowledge Translation, King Saud University Medical City, Riyadh, Saudi Arabia
[d] Family Medicine, Military Hospital Alhada, Taif, Saudi Arabia
[e] Clinical Pathology Board Residency Program, Ministry of Health, Saudi Arabia
[f] Intern, Clinical Pharmacy, King Saud University Medical City, Riyadh, Saudi Arabia
[g] Nursing Services Department, Occupational Health and Safety Clinic King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia

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ABSTRACT

The clinical improvement after assessing patients with cough variant asthma in outpatient clinics, and therapy success varied depending on the subjective improvement. Cough could be controlled within appropriate time and subsequent management can consist of inhaled corticosteroids. In this study we used the cough improvement, the only available clinical response, as a predictable factor to determine the effect of different modalities of treatment among patients with cough variant asthma. Retrospective observational analysis was performed in Saudi Arabia's King Saud University Medical City, on the presentation, diagnosis, course of therapy, and responsiveness to oral and inhaled steroids in patients with cough variant asthma. All patients who visited the clinic on multiple occasions with persistent, acute coughing without being pre-screened between September 2021 and September 2022 included based on medical records. Cough resembles cough variant asthma is the term used to describe a cough without a diagnosed etiology. To identify patients eligible for CVA treatment, iindividuals having GERD-associated cough, allergic rhinitis, bronchial asthma, smokers and atopic cough was excluded. For the examination of these findings, IBM SPSS version 28 (Armonk, NY, USA) was employed. As a result of using budesonide-formoterol inhaler, most patients (86.3 %) showed improvement in their cough symptoms (with 95 %CI: 78.3 to 94.9). There was a significant yet weak positive correlation between the frequency of cough symptoms before and after using budesonide-formoterol ($r = 0.318$, P value < 0.001). The understanding of treatment response and patient selection for budesonide-formoterol inhaler therapy, providing clinicians with valuable information to optimize patient care.

1. Introduction

Kantar et al. (2022) have recently shown that verifying the early therapy using the patient's history and test results is crucial for arriving at a definitive diagnosis of protracted acute cough. Morice et al. (2006) have recently shown that, given that there is presently no gold standard for diagnosis, determining the cause of a cough and choosing the optimum treatment in a clinic are difficult tasks. Spirometry is often employed in respiratory medicine, although it doesn't seem to be as effective in treating protracted acute cough, incorporating CVA, as it is in treating asthma and chronic obstructive pulmonary disease. (Kaplan, Stanbrook, 2010).

Cough variant asthma (CVA) ranks among the prevalent triggers of acute coughing. (Niimi, 2011) All types that mimic asthma but not

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E-mail addresses: Sarif@ksu.edu.sa (S. Ibrahim Arif), yamer@ksu.edu.sa (Y.S. Amer), aelmalky@ksu.edu.sa (T. Adnan Alkamal), mbinsaeed1.c@ksu.edu.sa (M. Abdulrahman Binsaeed), 437100407@student.ksu.edu.sa (B. Ibrahim Arif), Mdalbaqami@ksu.edu.sa (M. Dhaifallah Albaqami), ofahad@ksu.edu.sa (O. Bakri Alfahed).

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asthma, are treated with steroids, whether inhaler or systematic. (Reddel, 2022) For evaluation, clinical response was the available predictable and main outcome indicating patient improvement. (Niimi, 2021) This type of asthma phenotype is called cough variant asthma (CVA). Magni et al, (2010) have recently shown that CVA patients should have normal peak flow meter and spirometer. Individuals with CVA typically exhibit less airway sensitivity compared to those with classic asthma. So, PEFR, Spirometry, challenge tests and testing mucus eosinophils are inconclusive.

Early symptomatic treatment might prevent morbidity and complications of respiratory illness and help return back to work as fast as possible. Cough origin may be differentiated by history either; in morning with allergic rhinitis, after meals or lying bed in reflux diseases, at night or sleep time in CVA (asthma phenotype). All phenotypes of asthma include cough variant is diagnosed clinically. CVA is hard to be diagnosed, since acute cough can indicate many other conditions. It lacks several common asthma indicators, such as wheezing. Zhou et al, (2022) have recently shown that CVA can turn into classic asthma when miss-diagnosed or left untreated. The patient will begin to complain of wheezes and shortness of breath. The theory is founded on the evidence that cough-variant asthma (CVA) can be an early manifestation of classic asthma, with approximately 30 % of CVA patients later developing the classic form. Rouadi et al, (2021) have recently shown that however, CVA also differs from classic asthma in its higher propensity for spontaneous resolution compared to the more persistent nature of classic asthma.

Cough-variant asthma manifests solely with a dry, nonproductive chronic cough lasting over 8 weeks in adults or 4 weeks in children. Recent literature indicates CVA treatment mirrors classic asthma management. Holmes et al, (2022) have recently shown that for mild CVA, as-needed inhaled short-acting beta-agonists may suffice. More stubborn cases may necessitate daily inhaled corticosteroid controller medication. Some doctors actively strive to prevent CVA progression to classic asthma through aggressive upfront combination treatment to rapidly resolve the cough. Zhu et al, (2019) have recently shown that after cough resolution, continued daily inhaled corticosteroids may be warranted for some patients to prevent relapse, though evidence on optimal CVA management remains limited. Gibson et al, (2002) and Fujimura et al, (2005) have recently shown that patients with CVA reportedly have higher levels of eosinophils in their bronchoalveolar lavage (BAL) fluid, sputum and bronchial mucosal tissue, and the level of eosinophilia is correlated with the severity of the illness. Additionally, Leach et al, (2002) and Niimi et al, (1998) have recently shown that research using biopsy samples of the central airway mucosa and BAL fluid obtained from the parenchyma and peripheral airways have shown that the degree of eosinophilia is comparable between CVA and typical asthma. Takeda et al, (2010) and Carvalho et al, (2011) have recently shown ha CVA is regarded as a peripheral airway inflammatory illness comparable to asthma because it entails structural alterations, such as subepithelial thickness, goblet cell hyperplasia, and vascular proliferation that cause airway remodelling. Continuous asthma can develop in certain CVA instances.

Oppenheimer et al, (2007) have recently shown that in order to reduce inflammation and remodelling, it is advised to use inhaled corticosteroids (ICSs) as soon as possible. ICS has recently been commercially released in a number of particle sizes. Asthma treatment may differ slightly depending on the particle size and the site of the inflammation, according to certain research. (Shirai, 2018) On the other hand, there is disagreement on the appropriate ICS particle sizes to utilize for CVA therapy.

In this study we tried to use the cough improvement, the only available clinical response, as a predictable to determine the effect of different modalities of treatment among patients having cough variant asthma.

2. Methodology

Retrospective analysis was done for patients with cough variant asthma's appearance, diagnosis, treatment plan, and response to oral and inhaled steroids in retrospect. Retrospective observational research was conducted in the King Saud University Medical City in Riyadh, Saudi Arabia. Based on medical records, all patients with a acute persistent cough who attended the clinic in a row and without being prescreened between September 2021 and September 2022 was included. An acute cough that has any of the characteristic; Cough more at night, with shortness of breath, interrupting speech and meals, progressive in nature, persistent and interrupting sleep, included as early features of CVA. In order to select patients with CVA, individuals with post-infectious cough, GERD-associated cough, allergic rhinitis, atopic cough, smokers and bronchial asthma were excluded from the study.

In terms of patients environmental factors that may influence management of CVA, we tried to select our patients excluding any contributing factors hat may alleviate or exaggerate the manifestations of CVA such as; Allergen exposure (environmental allergens such as pollen, dust mites, pet dander, or mold), poor air quality, air pollution, pollutants such as particulate matter, ozone, and nitrogen dioxide), occupational exposures (workplace irritants or allergens), smoking, respiratory infections, climate and weather changes (cold air, or humidity fluctuations), allergic rhinitis, Gastroesophageal Reflux Disease (GERD), medication allergies and psychological stress.

The educational level of the patients were diploma, bachelor's degree, board certified, masters and PhDs. All of them were healthcare staff and healthcare providers.

No history to any of our patients for drug anaphylaxis or anaphylactic shock. We excluded from our population any patient had history of specific medications such as; Beta-Blockers, Aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Angiotensin-Converting Enzyme (ACE) Inhibitors, chemotherapy, psychiatric treatment, or for other medical conditions may have an impact on asthma symptoms. Those who take budesonide are excluded as background is asthma or COPD from exclusion criteria.

A 7-point Likert scale was used to evaluate symptoms or the effect of symptoms during the last two weeks in a questionnaire for the assessment of the clinical response in patient with characteristically cough. High scores will indicate a more favourable clinical response. This tool is quick, easy to use, repeatable, and well verified.

Within the scope of this study, a comprehensive analysis was conducted using Electronic Medical Records (EMR) data obtained from the occupational health and safety clinic (OHSC) at KSUMC. A total of 641 patient files were retrieved and reviewed, and subsequent telephone interview questionnaires were administered to gather additional information.

2.1. Statistical analysis

Statistical analysis was done by SPSS version 28 (IBM Co., Armonk, NY, USA). Categorical data were presented as frequency and percentage (%). Wilcoxon signed-rank test was used to analyze the frequency of cough symptoms before and after budesonide-formoterol use. Spearmen's rank correlation coefficient was calculated to estimate the degree of correlation between the frequency of cough symptoms before and after budesonide-formoterol use. Chi-square test was used to analyze the relation between the improvement in cough symptoms and their frequency after budesonide-formoterol use. Odds ratio was calculated to estimate the association between the frequency of cough symptoms before budesonide-formoterol and the probability of improvement in these symptoms after budesonide-formoterol use. A two tailed P-value < 0.05 was considered statistically significant.

3. Results

Out of 641 patient files retrieved from Electronic Medical Records (EMR) system from patients attending occupational health and safety clinic (OHSC) KSUMC, and after telephone interview questionnaires were conducted, 549 patients confirmed receiving budesonide-formoterol from the pharmacy, of whom, 497 confirmed using it. [Table 1].

Before using budesonide-formoterol, around half (52.1 %) of the 497 participants experienced cough symptoms including (waking them up at night, persistent continuous, more at night, disturbing speech or eating, with shortness of breath) more than 4 times (with 95 %CI: 46 to 58.9), 28.8 % experienced those symptoms 2 to 3 times (with 95 %CI: 24.3 to 33.9), 15.5 % experienced them 3 to 4 times (with 95 %CI: 12.2 to 19.4) and 3.6 % had them 1 to 2 times (with 95 %CI: 2.1 to 5.7). [Table 2].

After using budesonide-formoterol, most patients (76.9 %) experienced cough symptoms including (waking them up at night, persistent continuous, more at night, disturbing speech or eating, with shortness of breath) only 1 to 2 times (with 95 %CI: 69.4 to 85), 11.1 % experienced those symptoms 2 to 3 times (with 95 %CI: 8.3 to 14.4), 7 % experienced them 3 to 4 times (with 95 %CI: 4.9 to 9.8) and 5 % had them for more than 4 times (with 95 %CI: 3.3 to 7.4). [Table 3].

The comparison between the frequency of cough symptoms before and after using budesonide-formoterol revealed a statistically significant improvement after using budesonide-formoterol as patients elicited significantly less frequent symptoms than before using it (P value $<$ 0.001). [Table 4].

As a result of using budesonide-formoterol, most patients (86.3 %) showed improvement in their cough symptoms (with 95 %CI: 78.3 to 94.9). [Table 5].

There was a significant yet weak positive correlation between the frequency of cough symptoms before and after using budesonide-formoterol ($r = 0.318$, P value < 0.001) as summarized in Table 6.

There was a statistically significant relation between improvement in cough symptoms and their frequency after using budesonide-formoterol as patients who were improved manifested significantly less frequent cough symptoms than those not improving (P value < 0.001). [Table 7].

4. Discussion

Our study demonstrates the effectiveness and popularity of budesonide-formoterol as a treatment option in the occupational health and safety clinic. Ställberg et al, (2015) have recently shown that the high number of patients receiving the medication suggests a significant utilization of budesonide-formoterol inhaler in the clinical setting. Our results indicate a high compliance rate among the patients, as a large proportion of them continued to use the prescribed medication.

Kuna et al, (2007) have recently shown that the high number of patients receiving the medication and the significant proportion actively using it suggest its perceived efficacy and acceptance among the patient population. Such observations provide valuable insights for healthcare providers and researchers, allowing them to make informed decisions regarding treatment protocols and further investigations (see Table 8).

A significant proportion of participants reported experiencing cough

Table 1
Distribution of participants according to receiving budesonide-formoterol from the pharmacy and using it.

	N	%
Received		
Yes	549	85.6
No	56	8.7
Didn't remember	36	5.6
If received		
Used it	497	77.5
Didn't use it	52	8.1

Table 2
Frequency of cough symptoms before using budesonide-formoterol (n = 497).

	N	%	95 %CI of rate
1 – 2 times	18	3.6	2.1 to 5.7
2 – 3 times	143	28.8	24.3 to 33.9
3 – 4 times	77	15.5	12.2 to 19.4
>4 times	259	52.1	46 to 58.9

CI: Confidence interval.

Table 3
Frequency of cough symptoms after using budesonide-formoterol (n = 497).

	N	%	95 %CI of rate
1 – 2 times	382	76.9	69.4 to 85
2 – 3 times	55	11.1	8.3 to 14.4
3 – 4 times	35	7.0	4.9 to 9.8
>4 times	25	5.0	3.3 to 7.4

CI: Confidence interval.

Table 4
Comparison between the frequency of cough symptoms before and after using budesonide-formoterol (n = 497).

	Before budesonide-formoterol	After budesonide-formoterol	P value
1 – 2 times	18 (3.6 %)	382 (76.9 %)	<0.001*
2 – 3 times	143 (28.8 %)	55 (11.1 %)	
3 – 4 times	77 (15.5 %)	35 (7 %)	
>4 times	259 (52.1 %)	25 (5 %)	

Data are presented as frequency (%), *: Statistically significant as P value < 0.05.

Table 5
Improvement of cough symptoms after using budesonide-formoterol (n = 497).

	N	%	95 %CI of rate
Improvement			
Yes	429	86.3	78.3 to 94.9
No	68	13.7	10.6 to 17.4

CI: Confidence interval.

Table 6
Spearman's rank correlation between the frequency of cough symptoms before and after using budesonide-formoterol.

	Before budesonide-formoterol	
	r_s	P value
After budesonide-formoterol	0.318	<0.001*

r_s: Spearman's rank correlation coefficient, *: Statistically significant as P value < 0.05.

Table 7
Relation between the improvement in cough symptoms and their frequency after using budesonide-formoterol.

	Improvement		P value
	No (n = 68)	Yes (n = 429)	
After budesonide-formoterol			
1 – 2 times	20 (29.4 %)	362 (84.4 %)	<0.001*
2 – 3 times	7 (10.3 %)	48 (11.2 %)	
3 – 4 times	16 (23.5 %)	19 (4.4 %)	
>4 times	25 (36.8 %)	0 (0 %)	

Data are presented as frequency (%), *: Statistically significant as P value < 0.05.

Table 8
Odds ratio for association between the frequency of cough symptoms before using budesonide-formoterol and the improvement in those symptoms.

	Odds ratio	95 %CI	P value
Before budesonide-formoterol			
1 – 2 times	Ref		
2 – 3 times	793.33	78.08 to 8060.45	<0.001*
3 – 4 times	48.45	6.05 to 387.86	<0.001*
>4 times	140.25	17.97 to 1094.44	<0.001*

CI: Confidence interval, *: Statistically significant as P value < 0.05.

symptoms prior to using the medication. These symptoms included instances of coughing that occurred more than 4 times, which affected their sleep, persisted continuously, were more prominent at night, and interfered with speech or eating. However, there was a substantial impact of cough symptoms on the participants' daily lives and well-being. Vogelmeier et al, (2012) have recently shown that the frequency and severity of coughing episodes, particularly during sleep and activities such as speech and eating, indicate a significant disruption to their quality of life. This emphasizes the need for an effective treatment option to alleviate these symptoms and improve overall respiratory health.

The initiation of budesonide-formoterol treatment in this study presents a justifiable intervention for managing cough symptoms. Scichitano et al, (2004) have recently shown that budesonide is a corticosteroid that helps reduce airway inflammation, while formoterol is a long-acting bronchodilator that helps relax the airway muscles, thereby improving airflow. The combination of these two medications offers a comprehensive approach to address the underlying causes of cough symptoms, providing relief and improving respiratory function.

The results of this study underscore the effectiveness of budesonide-formoterol in managing cough symptoms. By assessing the prevalence and frequency of coughing episodes before treatment, we can establish a baseline for comparison and evaluate the impact of the medication on symptom reduction and overall respiratory healt. (Kuna, 2010).

Our findings reinforce the justification for using budesonide-formoterol inhaler as an effective treatment option for managing cough symptoms associated with respiratory conditions. The results demonstrate its ability to significantly reduce the frequency of coughing episodes and alleviate their impact on patients' daily lives, align with previous research demonstrating the efficacy of budesonide-formoterol in managing cough symptoms associated with respiratory conditions. Ställberg et al, (2008) have recently shown that budesonide, as a corticosteroid, has anti-inflammatory properties that reduce airway inflammation, while formoterol acts as a bronchodilator, relaxing the muscles in the airways and improving airflow. The combination of these two components provides a comprehensive approach to symptom relief.

The results of this study add to the existing body of evidence supporting the use of budesonide-formoterol in the management of cough symptoms. Buhl et al, (2012) have recently shown that the previous studies have demonstrated the effectiveness of this medication in various respiratory conditions characterized by cough, such as asthma and chronic obstructive pulmonary disease (COPD). Our findings further strengthen the case for budesonide-formoterol as a valuable therapeutic option in clinical practice.

The results of our study indicate a statistically significant yet weak positive correlation between the frequency of cough symptoms before and after the administration of budesonide-formoterol. Ställberg et al, (2015) have recently shown that the correlation coefficient indicates a positive association between the pre-treatment and post-treatment frequencies of cough symptoms. However, the weak strength of the correlation suggests that other factors may also contribute to the variability in symptom improvement following budesonide-formoterol administration.

Several justifications can be proposed to explain the observed correlation. Firstly, it is important to note that budesonide-formoterol is primarily indicated for the management of respiratory conditions related with cough, such as asthma and chronic obstructive pulmonary disease (COPD). As a result, patients with more severe cough symptoms prior to treatment may have a higher likelihood of experiencing a greater improvement in symptoms compared to those with milder symptoms. Lalloo et al, (2003) have recently shown that this could explain the positive correlation between pre- and post-treatment symptom frequencies.

Furthermore, the correlation between pre- and post-treatment symptom frequencies may also be influenced by individual patient characteristics and disease-related factors. For example, patients with more advanced respiratory diseases or underlying comorbidities may exhibit a higher burden of cough symptoms, which could impact their response to treatment. Additionally, Hardy et al, (2019) have recently shown that treatment adherence and medication dosage may vary among patients, which can influence the effectiveness of budesonide-formoterol in reducing cough symptoms.

It is worth noting that while the correlation between pre- and post-treatment symptom frequencies is statistically significant, the weak strength of the correlation suggests that factors other than the initial symptom frequency may also play a vital role in determining the response to budesonide-formoterol. Bateman et al, (2011) stated that these factors could include genetic variations, individual patient responses to medication, and environmental factors, among others. Further research is warranted to explore these contributing factors and better understand the complex relationship between pre-treatment symptom severity and treatment outcomes.

Patients who experienced more frequent cough symptoms prior to initiating budesonide-formoterol treatment likely had more severe underlying respiratory conditions. The higher frequency of coughing episodes could be indicative of increased airway inflammation and bronchoconstriction. As a result, these patients may have presented a greater therapeutic target for budesonide-formoterol, leading to a higher likelihood of improvement in cough symptoms.
(Sears, Radner, 2009).

4.1. Recommendations

Further research is needed to explore additional factors that may influence the response to budesonide-formoterol inhaler and to identify predictors of treatment outcomes. Long-term studies assessing the sustained efficacy and safety of budesonide-formoterol in larger and more diverse patient populations would provide valuable insights into its clinical utility. Ultimately, a comprehensive understanding of the correlation between pre-treatment symptom severity and treatment response will contribute to optimizing patient care and improving outcomes in the management of cough symptoms.

Further research is warranted to explore the underlying mechanisms driving the relationship between improvement in cough symptoms and their frequency following budesonide-formoterol treatment. Additionally, long-term studies involving larger patient populations and extended follow-up periods would provide valuable insights into the sustained efficacy and safety of budesonide-formoterol in managing cough symptoms.

4.2. Clinical implication

These findings have important clinical implications, as they provide valuable insights into patient selection and treatment strategies for managing cough symptoms in respiratory conditions. Healthcare professionals can utilize the baseline frequency of cough symptoms as a prognostic indicator to identify patients who are more likely to benefit from budesonide-formoterol therapy. The decrease in cough symptom frequency after budesonide-formoterol treatment is an important observation with significant clinical implications. Patients experienced

significantly fewer coughing episodes, indicating a positive therapeutic response to the medication. This improvement suggests that budesonide-formoterol effectively targets and addresses the underlying causes of cough symptoms, such as airway inflammation and bronchoconstriction.

These findings have important clinical implications, suggesting that monitoring and assessing the frequency of cough symptoms can serve as a valuable indicator of treatment response to budesonide-formoterol. Healthcare professionals can utilize this information to evaluate the effectiveness of the medication and make informed decisions regarding the management of cough symptoms in patients with respiratory conditions.

4.3. Research limitations

The study's limitations include a specific population and retrospective design, which may limit generalizability to broader patient populations. The data used in the analysis relies on self-reported information from telephone interviews, which may introduce biases and confounding factors. Future research could incorporate additional methodologies, such as medical record reviews or objective measurements, to strengthen the reliability of the findings. Factors such as environmental triggers or comorbidities were not specifically assessed in the study, but they could contribute to cough symptoms. The assessment of cough symptom frequency relied on patient self-reporting, which may introduce bias or subjective interpretation. Objective measures, such as cough monitoring devices or clinician assessments, could provide additional insights and validation of reported improvements. The study's sample size and diverse patient population should also be considered when interpreting the results.

4.4. Research validation

To further validate our results and enhance their generalizability, future research should involve larger and more diverse patient cohorts, as well as prospective study designs. Long-term studies assessing the sustained efficacy and safety of budesonide-formoterol in managing cough symptoms would also provide valuable insights into its clinical utility.

Conclusion

The study found a significant association between the frequency of cough symptoms before using budesonide-formoterol inhaler and the subsequent improvement observed after its administration. Patients with more frequent cough symptoms at baseline exhibit higher odds of improvement, highlighting the potential of budesonide-formoterol as an effective therapeutic option for managing cough symptoms in acute respiratory conditions. Healthcare professionals can consider budesonide-formoterol as a viable treatment option, taking into account individual patient characteristics and the overall efficacy demonstrated in the study. Further research and clinical trials are needed to explore the long-term benefits, safety profile, and optimal dosing strategies of budesonide-formoterol in different patient populations. The findings contribute to the existing knowledge base and support the implementation of budesonide-formoterol as an effective therapeutic option for individuals experiencing acute cough symptoms associated with respiratory conditions. Further research is warranted to explore the sustained benefits and safety profile of budesonide-formoterol treatment in diverse patient populations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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