RESULTS OF ASTHMA CONTROL WITH INHALED CORTICOSTEROID AND LONG ACTING β2 ADRENERGIC AGONIST IN 3 MONTHS

Nguyen Giang Nam[1]; Ta Ba Thang[2]; Nguyen Van Doan[3]

SUMMARY

Asthma control is the primary treatment for asthma patients. Use of an inhaled corticosteroid and a long acting β2 adrenergic agonist has been proven to be effective in asthma control. Objectives: To evaluate results of bronchial asthmatic control by inhaled corticosteroid and long acting β2 adrenergic agonist in 3 months. Subjects and methods: 84 patients diagnosed with asthma and treated completely acute exacerbations and managed at Asthma Counseling Unit, Center of *Allergology and Clinical Immunology*, *Bachmai Hospital from August 2014 to August 2016. The patients were controlled by inhaled corticosteroid and long acting β2 adrenergic agonist with dosages corresponding to the degrees of disease*. *Serum levels of interleukine-4, interleukine-13 were tested by immunofluorescence method on IMMULITE 1000 system. Results and conclusion: The rates of controlled patients significantly increased with the rates of 36.9%, 79.8% and 82.1%, respectively. The proportion of partly controlled and uncontroled patients tended to decrease. Patients with normal BMI and asthmatic level I, II had higher controlled levels (p < 0.05). FEV_1 and FEV_1/FVC increased, serum interleukine-13 levels significantly decreased according to the level of asthma control.*

** Keywords: Asthma control; Inhaled corticosteroid; Acting β2 adrenergic agonist.*

INTRODUCTION

Bronchial asthma (BA) is a common disease in the world and tends to increase worldwide [8]. According to statistics of the World Health Organization, every 10 years, the prevalence of the asthma increased by 20 - 50%, especially in the past 20 years [8]. An inflammatory response is an important pathogenesis mechanism in BA. The characteristics of the asthma is heterogeneous and clinical manifestations by the outbreak of asthma. Asthma control is the primary treatment for patients with BA [7]. Use of an inhaled corticosteroid (ICS) and a long acting β2 adrenergic agonist (LABA) has been proven to be effective in control of BA: reducing the incidence and severity of asthma, improving clinical symptoms, respiratory function and quality of life for patients [11]. In the global strategy for bronchial asthma, ICS has been used to treat BA from stage II. However, the timing, dosage and duration of ICS use in BA treatment are controversial [8].

1. Thainguyen Medical College

2. 103 Military Hospital

3. Bachmai Hospital

Corresponding author: Nguyen Giang Nam (phuyenpathfirder@gmail.com)

Date received: 20/02/2019

Date accepted: 18/04/201

This research aims: *To evaluate the results of bronchial asthmatic control by ICS and LABA in 3 months at Center of Allergology and Clinical Immunology*, *Bachmai Hospital.*

SUBJECTS AND METHODS

1. Subjects.

There were a total of 84 patients diagnosed with BA and treated completely acute exacerbations, in which the average age was 44.58 ± 16.8 (the lowest was 16, the highest was 77 years old) and managed at Asthma Counseling Unit, Center of Allergology and Clinical Immunology, Bachmai Hospital from August 2014 to August 2016.

* *Selection criteria*:

Diagnosis of asthma according to the GINA guideline (2012), without acute exacerbations, adherence to treatment, asthma controlled by ICS and LABA with dosages corresponding to the degrees of disease (based on the asthma degrees) according to GINA guideline, acceptance of monthly examination and testing indicated by doctors.

** Exclusion criteria:*

Acute asthma exacerbation, acute bacterial rhinosinusitis, other respiratory diseases, non-compliance with ICS and LABA control therapy and no acceptance of research.

2. Method.

- A descriptive, prospective and longitudinal study. Patients were interviewed and done clinical examination at the times of study: it was pre-treatment of control and after 1, 2 and 3 months of asthma control.

- Classification of asthma degrees: According to GINA guideline (2016): I, II, III, IV levels from each time of evaluation: pre-treatment of control and after 1, 2 and 3 months of control. Doses of asthma control with ICS and LABA: According to GINA guideline (2016) are adjusted monthly to asthma stages. Patients with acute exacerbations should be used ventolin inhaler 300 µg/dose and repeated every 15 - 20 minutes. If symptoms were not relieved, they would be taken to hospital for treatment.

Tests of serum levels of interleukins: Serum levels of IL-4, IL-13 were tested by immunofluorescence method on IMMULITE 1000 system at Department of Immunology (Military Medical University) at times of pre-treatment of control and after 1, 2 and 3 months of control. Reference threshold of normal value of serum IL-4 and IL-13 levels was based on reference value of test kit and other research results.

The evaluation of asthma control was according to GINA guideline (2012).

The data are managed and processed on SPSS 12.0.

RESULTS AND DISCUSSION

1. General characteristics of the patients.

Table 1: Age and gender.

Gender / Age	Male		Female		Total	
	n	%	n	%	n	%
< 20	1	1.2	2	2.4	3	3.6
20 - 29	4	4.8	11	13.1	15	17.9
30 - 39	11	13.1	12	14.3	23	27.4
40 - 49	2	2.4	5	6.0	7	8.3
50 - 59	3	3.6	15	17.9	18	21.4
≥ 60	6	7.2	12	14.3	18	21.4
Total	27	32.1	57	67.9	84	100
X ± SD	44.58 ± 16.8					

Mean age of the patients was 44.58 ± 16.8 years (the lowest was 16, the highest was 77 years old), of which the age group of 20 - 59 accounted for the highest age group (75%) and the 20 - 59 years old group was the lowest age group (3.6%). The asthma rate in women (67.9%) was higher than men, accounting for 32.1%. Studies show that BA can occur at any age, but the majority was young people: in Nguyen Van Doan et al's study (2011), the results showed that asthma in patients aged 21 - 40 was 26% [1]. Chi C.H et al (2016) showed that asthma occured in patients aged 24 - 58 years [6]. Our research results show that there were 67.9% of females and 32.1% of males, which was similar to other studies, Le Thi Tuyet Lan and Huynh Anh Kiet (2013) conducted a study on 108 asthma patients at Respiratory Clinic, Hochiminh City University of Medicine and Pharmacy, their findings revealed that the prevalence of asthma found in women was 65.74% and 34.26% in men [2].

Table 2: Some characteristics of patients before the asthma control.

Characteristics / Number of patients	n	%
Severity of asthma:		
Level I	9	10.7
Level II	33	39.3
Level III	19	22.6
Level IV	23	27.4

Lung function:		
FEV_1	48.16 ± 13.37	
FEV_1/FVC	57.94 ± 13.82	
Blood leucocystes:		
Leukocytosis	41	62.1
Increase N	33	50
Increase E	7	10.6

** Level of disease:*

Rate of asthma patients at level II, level IV, level III and level I accounted for 39.3% (the highest rate), 27.4%, 22.6% and 10.7% (the lowest rate), respectively. Chu Thi Cuc Huong (2008) showed that level III and IV was mainly predominant accounting for 41.5% and 30.9%, respectively. Le Thi Tuyet Lan et al (2013) showed that the majority was asthma level I occupying 43.52% [2]. Reed C.E (2012) revealed that the majority was asthma level III and IV higher than asthma level l, II.

** Pulmonary ventilation*:

Mean values of both FEV_1 and FEV_1/FVC ratio also decreased. According to Ohwada A (2011), mean FEV_1 initial value was 88.96 ± 13.12%. It was estimated that FEV_1/FVC ratio was 80.47 ± 8.86%. An analytical research on 23 bronchial asthma patients used by ICS for 12 weeks, before treatment, the results showed that FEV_1 (79.01 ± 17.89%) and FEV_1/FVC (65.86 ± 10.28%) all fell below normal level [6]. According to Birajdar G et al (2017), FEV_1 (L) and FEV_1/FVC ratio were 1.3 ± 0.72% and 69.37 ± 18.16%, respectively. Ventilation in our patients also corresponded to severe asthma (level II - IV).

- Blood formula:

Blood cells involved in inflammatory reactions to the respiratory tract of asthma patients include polymorphonuclear leukocytes and eosinophils [10]. Le Thi Thu Huong's study (2017) revealed that asthma patients with leukocytosis, polymorphonuclear leucocytosis and eosinophilia accounted for 81.6%, 66.4% and 32%, respectively. Nguyen Thi Dieu Thuy's study (2015) showed that there were 81.7% of patients with leukocytosis, of which patients with polymorphonuclear leucocytosis and eosinophilia accounted for 54.8% and 30.4%. In our study, rates of patients with leukocytosis, polymorphonuclear leukocytes and eosinophilia were lower compared to abovesaid authors' findings with the corresponding rate of 62.1%, 50% and 10%, respectively.

Some studies have shown that inhaled corticosteroids reduced the number of eosinophils in sputum in adult asthmatic patients, but did not affect the total cells, epithelial cells, polymorphonuclear cells or lymphocytes. Our asthmatic patients admitted to the hospital were all given corticosteroids during their treatment.

2. Results of control treatment.

Table 3: Results of control treatment after 1, 2 and 3 months of control (n = 84).

Time / Level of control	Pre-treatment (1)		After one month (2)		After two months (3)		After three months (4)	
	n	%	n	%	n	%	n	%
Controled asthma	4	4.8	31	36.9	67	79.8	69	82.1
Partly controlled asthma	38	45.2	38	45.2	15	17.9	8	9.5
Uncontroled asthma	42	50.0	15	17.9	2	2.4	7	8.3
p* (* *Chi-squared test*)			$p_{1\&2} < 0.05$		$p_{2\&3} < 0.05$		$p_{3\&4} < 0.05$	

** Results of asthma control:*

Results of well-controlled patients increased gradually after 1, 2 and 3 months with the corresponding rate of 82.1%, 79.8% and 36.9% respectively, which significantly increased compared to pre-treatment. The number of patients with partly and uncontrolled patients significantly reduced after 3 months of treatment. However, 8.3% of patients still did not achieve control level. The difference was statistically singificant with $p < 0.05$. According to Vu Thi Hong (2015), after 3 - 6 months of controlled treament with ICS and LABA, well controlled and partially controlled asthma increased gradually. The rate of uncontrolled asthma decreased compared to pre-treatment asthma with $p < 0.05$. Nguyen Hoang Phuong's study (2018) revealed that during treatment process at 3 months, 6 months and 12 months, rates of patients with bronchial asthma controlled by ICS and LABA tended to increase gradually and accounted for 10%, 33.33% and 85%, respectively, compared to pre-treatment [4]. O'Byrne et al (2005) revealed that asthma control was significantly improved after combining ICS and LABA.

Table 4: The relationship between level of control and clinical characteristics after 3 months of treatment (n = 84).

Clinical characteristics / Control level		Controlled (1)		Partial (2)		Uncontrolled (3)		p*
		n	%	n	%	n	%	
BMI	Obesity	8	9.5	1	1.2	5	6.0	< 0.05
	Normal	58	69.0	6	7.1	2	2.4	
	Skinny	3	3.6	1	1.2	0	0.0	
	(X ± SD)	21.19 ± 2.62		21.34 ± 2.62		24.46 ± 2.77		
Onset	Early	18	21.4	2	2.4	0	0.0	> 0.05
	Late	51	60.7	6	7.1	7	8.3	

Asthma level	I	69	82.1	5	6.0	0	0.0	< 0.05
	II	0	0.0	3	3.6	0	0.0	
	III	0	0.0	0	0.0	3	3.6	
	IV	0	0.0	0	0.0	4	4.8	

** Relationship between control level and clinical characteristics:*

There was a difference in BMI with control levels: the uncontrolled rate in obese patients was higher than that in normal and thin people (6% compared to 2.4%) with $p < 0.05$. There was only a low rate of partial control (3.6 - 6%) in patients with levels I and II. In contrast, rates of the uncontrolled patients at level III and IV after 3 months of treatments was 3.6% to 4.8% ($p < 0.05$). According to Shannon Novosad S et al's study (2013), leptin increased and adiponectin decreased in obese patients that was more difficult to asthma control. According to GINA (2016), late-onset asthma is more likely to be non-allergic and requires higher-dose ICS or no response to corticosteroids, which makes asthma more difficult to control [9]. Multivariate analysis by Hsu J.Y et al (2014) showed that there was a correlation between decreased lung function and asthma control with duration of disease ($p < 0.001$) [14]. Our results did not find the relationship between onset of disease and control levels ($p > 0.05$).

** Relationship between control level and asthma level:*

The study results show that after 3 months of treatment, rates of completely controlled asthma level I increased by 82.1%; patially controlled asthma level I, II decreased (accounting for 9.6%), the uncontrolled asthma level III and IV accounted for 8.4% ($p < 0.05$). Nelson H.S et al studied 447 asthma patients after 3 months of treatment with fluticasone propionate and salmeterol, the results of patient group treated by fluticasone propionate + salmeterol were better controlled, the severity of asthma was 2% lower than that of group treated fluticasone propionate + montelukast (6%) [12].

Table 5: The relationship between control level and FEV_1, FEV_1/FVC after 3 months of control (n = 84).

Control level / X ± SD	Completed (n = 69)	Partial (n = 8)	Uncontrolled (n = 7)	p*
FEV_1	86.12 ± 12.98	83.31 ± 11.35	57.72 ± 22.43	< 0.05
FEV_1/ FVC	88.98 ± 21.27	86.99 ± 12.89	69.07 ± 21.27	< 0.05

After 3 months of control, mean values of FEV_1 and FEV_1/FVC ratio also increased significantly according to control levels ($p < 0.05$). Chi C.H et al's study (2016), after 3 months of ICS treatment revealed that pulmonary ventilation parameters increased compared to before treatment with significance ($p < 0.001$) [6].

Table 6: Relationship between control level and serum IL-4 (n = 66).

Control level \ IL-4 (pg/mL)		< 8		≥ 8		p*
		n	%	n	%	
After 1 month	Controled	20	30.3	0	0	> 0.05
	Partly controled	31	47	1	1.5	
	Uncontrolled	13	19.7	1	1.5	
After 2 months	Controled	53	80.3	0	0	> 0.05
	Partly controled	11	16.7	0	0	
	Uncontrolled	2	3.0	0	0	
After 3 months	Controled	52	78.8	1	1.5	> 0.05
	Partly controled	6	9.1	0	0	
	Uncontrolled	7	10.6	0	0	

There was no significant difference in changes in serum IL-4 levels according to control levels after 1, 2 and 3 months of treatment, with p > 0.05. Lee Y.C (2001) revealed that there was a relation between serum IL-4 level of acute asthma patients and partially controlled bronchial and complete control asthma, with p < 0.001. Brown K.R et al (2017) showed that there was a significant difference in IL-4 level between controlled and uncontrolled asthma with p = 0.03 [5].

Table 7: Relationship between control level and IL-13 level (n = 66).

Control level \ IL-13 (pg/mL)		< 9		≥ 9		p*
		n	%	n	%	
After 1 month	Controled	13	19.7	7	10.6	> 0.05
	Partly controled	13	19.7	19	28.8	
	Uncontrolled	6	9.09	8	12.1	
After 2 months	Controled	53	80.3	0	0	< 0.05
	Partly controled	11	16.7	0	0	
	Uncontrolled	2	3.0	0	0	
After 3 months	Controled	50	75.8	3	4.5	< 0.05
	Partly controled	6	9.1	0	0	
	Uncontrolled	4	6.1	3	4.5	

After 1 and 2 months of treatment, there was no statistically significant difference in IL-13 levels under control levels. After 3 months of treatment, the proportion of patients decreasing IL-13 levels in parallel with the level of complete control with statistically significant difference (p < 0.05).

According to Brown K.R et al (2017), there was a significant difference in IL-13 levels between controlled and uncontrolled asthma (p = 0.03) [5]. Janeva E.J et al

(2015) showed that IL-13 level after 6 months of ICS and LABA treatment decreased and improved clinical symptoms and gained a good control for patients. Joseph J (2004) revealed that median serum level of IL-13 in patients regularly using ICS was significantly higher than controlled asthma ($p < 0.003$).

CONCLUSION

Results of control treatment with ICS and LABA for asthma patients after 3 months of treatment, we gained the following results:

- Rates of well-controlled patients significantly increased 36.9%, 79.8% and 82.1%, respectively. The number of controlled partially and uncontrollable patients has tended to decrease.

- Patients with normal BMI and asthmatic level I, II had higher asthmatic control rates. There was a statistically significant difference with $p < 0.05$.

- FEV_1 and FEV_1/FVC ratio increased with control levels, serum IL-13 levels significantly decreased according to the level of asthma control.

REFERENCES

1. Nguyen Van Doan et al. Study on the status of bronchial asthma in Vietnam 2009 - 2011. Scientific and Technological Project of Ministerial level. Hanoi. 2011.

2. Le Thi Tuyet Lan, Huynh Anh Kiet. The correlation between bronchial asthma control level according to ACT and the health-related quality of life according to AQLQ (S). Hochiminh City Medicine. Topics of Internal Medicine I. 2013, Vol. 17, Supplement No.1, pp.137-141.

3. Ta Ba Thang. Bronchial asthma. Respiratory Diseases. The People's Army Publishing House. Hanoi. 2012, pp.13-41.

4. Nguyen Hoang Phuong. Treatment of allergic asthma caused by dermatophagoides pteronys sinus allergens with specific immunotherapy by sublingual route. Docteral Thesis in Medicine. Hanoi Medical University. 2018.

5. Brown K.R, Krouse R.Z, Calatroni A, Visness C.M, Sivaprasad U, Kercsmar C.M et al. Endotypes of difficult-to-control asthma in inner-city African American children. 2017, 12 (7).

6. Chi C.H, Liao J.P, Zhao Y.N et al. Effect of inhaled budesonide on IL-4 and IL-6 in exhaled breath condensate of asthmatic patients. Chinese Medical Journal. 2016, pp.819-823.

7. Janeva E.J, Goseva Z et al. The effect of combined therapy ICS/LABA and ICS/LABA plus montelukast in patients with uncontrolled severe persistent asthma based on the serum IL-13 and FEV_1. Open Access Macedonian Journal of Medical Sciences. 2015, 3 (2), pp.268-272. Global Strategy for Asthma Management and Prevention (2016 update).

8. Holguin F, Bleecker A.R, Buss W.W et al. Obesity and asthma: an association modified by age of asthma onset. J Allergy Clin Immunol. 2011, June, 127 (6), pp.1486-1493.

9. Barnes P.J. Pathophysiology of Asthma, chapter 5. Eur Respir Mon. 2003, pp.84-103.

10. Sobande P.O, Kercsmar C.M. Inhaled corticosteroids in asthma management. Respir. 2008, 53 (5), pp.652-633.

10. Nelson H.S, Busse W.W, Kerwin E et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticocorticoid plus montelukast. J Allergy Clin Immunol. 2000, 106 (6), pp.1088-95.

11. Novosad S, Khan S, Wolfe B et al. Role of obesity in asthma control. Obesity-asthma phenotype. Journal of Allergy. 2013, pp1-9.

12. Hsu J.Y, Vua S.L, Kuo B.I et al. Age of onset and the characteristics of asthma. Respirology. 2014, Aug, 9 (3), pp.369-372.