Medical Science

Assessment of control of bronchial asthma persistence and basic anti-inflammatory therapy volume control: School patients dynamic longitudinal monitoring results

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DISCOVERY

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ABSTRACT

The task was to study the characteristics of the control of symptoms of the disease at school age in order to improve the management of bronchial asthma in children. The study was conducted within the framework of the project of longitudinal monitoring of children's cohort formed by simple random sampling, which lasted 5 years. The control of the symptoms of the disease, the severity of the course and the response to the prescribed basic anti-inflammatory therapy were evaluated. The study covered 196 school children suffering from asthma in the non-attack period. The monitoring showed a significant 2.12-fold increase in the proportion of controlled asthma in the total cohort of patients, a statistically valid increase in the proportion of patients with low asthma control by 2.3-fold and a 1.9-fold decrease in the number of patients with partially controlled symptoms. The study showed that the proportion of patients with controlled persistent bronchial asthma during the observation period, according to the clinical-instrumental assessment scale, compared with the initial data, statistically reliably increased by 2.54 times. During the dynamic monitoring using the GINA questionnaire and the clinical-instrumental evaluation scale, a decrease in the proportion of uncontrolled asthma was revealed, contrary to the data of the AST test, which showed an increase in the number of such patients.

Keywords: Bronchial asthma, GINA, children, anti-inflammatory therapy, longitudinal monitoring

1. INTRODUCTION

Inhalation therapy is a necessary component of the treatment of bronchial asthma (BA) in children (Goralski et al., 2014), acting as a key basis for anti-inflammatory therapy strategy according to the guidelines of the Global

Initiative for the Treatment and Prevention of BA (GINA) (GINA Report, 2014). All modern regulatory documents stipulate that the treatment of asthma can be effective only by improving the management of the disease and achieving the optimal level of control due to the least sufficient amount of inhaled anti-inflammatory drugs (Vasbinder et al., 2013; Bosnic-Anticevich et al., 2014), Although the long-term goal of asthma treatment is to control symptoms and reduce exacerbations (GINA 2016; Smeele et al., 2007), researchers believe that the actual level of clinical control of asthma in Europe has not been achieved (Rabe et al., 20004; Chapman et al., 2008; Gold et al., 2012).

A partial reason for the failure to achieve this goal is the heterogeneity of the disease, while treatment guidelines in accordance with the current instructions are not personalized according to the individual patient (Khusial et al., 2017).

Inhalation treatment has many advantages, such as direct rapid onset of effect due to local delivery of high concentrations of the drug to the airways with minimal systemic side effects, but the use of these drugs leads to treatment ineffectiveness (Chapman et al., 2008; GINA 2016) poor control of asthma symptoms, frequent exacerbations, increasing the level of hospitalization and the cost of treatment (Vasbinder et al., 2013; Melani et al., 2011; Al-Jahdali et al., 2013; Uijen et al., 2009; Baddar et al., 2014).

The systematic review (Alzahrani et al., 2016) examined the tools used to assess the control of asthma symptoms in pediatric practice, in terms of their ability to effectively reflect the general state of control of asthma symptoms, including asthma control test (ACT), asthma control test for children (cACT), Asthma Control Questionnaire (ACQ), Asthma Therapy Assessment Questionnaire (ATAQ) and Symptom Scale (LASS). It has been shown that currently cACT and ACT are the only tools for assessing asthma symptoms used in pediatrics, with cACT being used for children aged 4–11 years and ACT for children aged 12–17 years (Revicki et al., 2006; Nathan et al., 2004; Liu et al., 2007). The advantages of the cACT questionnaire as an effective tool for controlling the symptoms of asthma in childhood are shown. The cAST questionnaire was developed in 2006 for self-assessment of asthma control in children aged 4 to 11 years for the previous 4 weeks. The questionnaire contains 7 questions (four for a child - 4 points each, three for parents - 6 points each), and the total ranges from 0 (poor asthma control) to 27 (complete asthma control) (Liu et al., 2007).

Like cACT, ACT is a multidimensional, standardized, proven, and most widely used tool for assessing asthma control in patients over 12 years of age. The ACT quantifies asthma control as a continuous variable and provides a numerical value for distinguishing between controlled and uncontrolled asthma. ACT is a 5-question questionnaire that reflects patients' self-assessment of symptoms (night and day), the use of emergency medications, limitation of daily activity due to asthma, and the patient's perception of asthma control over the past 4 weeks. Each answer to the question is rated on a 5-point scale so that the amount ranges from 5 (poor asthma control) to 25 (complete asthma control) (Revicki et al., 2006; Nathan et al., 2004). Thus, cACT and ACT are recommended to be used to assess the control of childhood asthma symptoms in a holistic framework (Alzahrani et al., 2016; Revicki et al., 2006; Nathan et al., 2004; Liu et al., 2007), which became the goal of our work.

The aim of the research is to improve the management of bronchial asthma in children, to study the characteristics of symptoms control of school-age disease during longitudinal monitoring of patients.

2. MATERIAL AND METHODS

Longitudinal monitoring of 196 school-age children (9.54 ± 0.26 years) with persistent bronchial asthma was performed by the prospective cohort method. The study was conducted not in the exacerbation phase of asthma for 5 years (from January 2014 till December 2019) with an assessment of control over the symptoms of the disease, severity and response to prescribed basic anti-inflammatory therapy. 196 patients underwent the initial examination, then 176 (10.20%), 160 (18.37%), 145 (26.02%) and 119 (39.29%) patients, respectively, were examined on repeated annual visits during the monitoring period. This decrease in the number of patients on visits was explained by dropping out of school age and a decrease in patient compliance as they grew older.

The initial examination revealed a predominance of male patients (63.78%) compared to girls (36.22%, P<0.001), which coincides with the literature on the predominant hypersensitivity in boys to puberty (Sennhauser et al., 1995). The surveyed cohort of patients at the place of residence was divided approximately in half: 42.35% lived in urban settlements and 57.65% - in rural areas (P<0.05), which reflected the service area of the Regional Children's Clinical Hospital in Chernivtsi, where patient's visits were made. The average history of bronchial asthma in the cohort was 3.99 ± 0.26 year, the average number of exacerbations in the anamnesis 8.39 ± 0.49 times and hospitalizations – 7.56 ± 0.52 times.

Ethical committee approval code & details

The research protocol and informed consent form were approved by the Commission on Biomedical ethics in biomedical scientific research of the Higher State Educational Establishment of Ukraine «Bukovinian State Medical University» (Minutes No. 36 dated 17.11.2016). The article is recommended for publication by the Commission on Biomedical ethics in biomedical scientific research of

the Higher State Educational Establishment of Ukraine «Bukovinian State Medical University» the protocol No. 4 dated 22 December 2020. The study was conducted in the design of longitudinal monitoring of child cohorts formed by simple random sampling, the duration of which was 5 years.

The level of control was determined by clinical and anamnestic indicators proposed by GINA-2006 and its subsequent versions. Controlled bronchial asthma (CBA) meant the absence of nocturnal symptoms and limited physical activity in patients for 12 weeks, the presence of no more than two episodes of diurnal asthma symptoms per week and the use of β2-agonists, FEV1 above 80% of the age norm, no exacerbations during the year. Lack of disease control was reported in the presence of three or more characteristics over the last 12 weeks, including: limited physical activity, nocturnal episodes of asthma, more than two daytime asthma symptoms using fast-acting β2-adrenomimetics, FEV1 below 80%, at least one exacerbation during the year. Partially controlled bronchial asthma was diagnosed in the presence of no more than three indicators characteristic of uncontrolled bronchial asthma.

Scoring control of asthma symptoms was performed by ACT test. A total score of more than 20 indicated complete control, 16 to 19 points indicated partial control, and 15 or less indicated no control of the disease. Thus, the loss of control in the dynamics was identified by a decrease in the sum of ACT test scores, and the improvement of control over asthma, on the contrary, by an increase in the sum of test scores during the final visit. The GINA test contains six questions with alternative answers. Absence of day and night symptoms, physical limitations and exacerbations, use of fast-acting inhalers less than 2 times a week and FEV1 above 80% were evaluated in one point. Conversely, two points were calculated in the presence of the above characteristics and the level of FEV1, which did not exceed 80% of the age norm. Thus, the sum of 6 points indicated complete control over the disease, 7-9 points – about partial control, and above 9 points - about uncontrolled bronchial asthma.

Clinical and instrumental assessment of the control level included 7 questions that reflected the symptoms of the disease (each question was evaluated from 0 to 4 points), as well as indicators of external respiratory function - FEV1 and PEF were determined. Ten or lower scores allowed to identify CBA, 11-16 points were associated with partial, and above 17 points - with uncontrolled variant of asthma. The decrease in the sum of GINA test scores and clinical-instrumental assessment of the control level in the dynamics confirmed the improvement of disease control, and the increase, on the contrary, the loss of control over symptoms.

The obtained results were analyzed by means of computer packages Statistica 6.0 Stat Soft Inc. and Excel XP for Windows using parametric and nonparametric calculation methods. Assessment of the diagnostic value of the test was carried out taking into account its specifics, the likelihood ratio and post-test probability of the event with positive and negative results, and the risk of event realization were assessed considering the ratio of chances and attributive risk. The study started after obtaining the informed consent of the patient and parents to participate in it following the adoption of the surveillance protocol by the local bioethical committee of the Regional Children's Clinical Hospital in Chernivtsi.

The work was carried out at the expense of the state budget of Ukraine, which was allocated for the implementation of the initiative research work "Genetic determination of preventive approaches in bronchial asthma in children", state registration number 0114U002471.

3. RESULTS

At the initial examination of patients there was no statistically significant predominance of the atopic form of bronchial asthma, which occurred in 53.57% of cases (P>0.05). The incidence of comorbid allergic rhinitis at the initial examination was 13.77%, and at the final visit it increased fourfold and amounted to 56.63% of observations (P<0.001). In the dynamics of longitudinal follow-up visits to children with bronchial asthma, the severity of the disease was determined, the results of which are shown in table 1.

Table 1 Frequency of registration (%) of severity degrees of persistent bronchial asthma in children in the dynamics of monitoring

Visits	Mild course	Moderate course	Severe course
Initial visit	10.20	50.0	39.80
I visit	7.78	50.0	42.22
II visit	9.21	40.79	50.0*
III visit	12.10	44.36	43.55
Final visit	14.43	52.06	33.51

Note: * - P<0.05 relative to the final visit

Thus, during the entire period of dynamic monitoring significant changes in the severity of asthma in the cohort of patients did not occur. At all visits, patients with mild persistent asthma accounted for the smallest proportion, and the subpopulation of

children with severe asthma ranged from 1/3 to half of the patients. Based on this, we made an assumption about the predominant value of control over the symptoms of bronchial asthma in planning the scope of basic treatment. The generalized results of the assessment of the asthma symptoms control according to the ACT questionnaire during longitudinal monitoring of children with asthma are shown in figure 1.
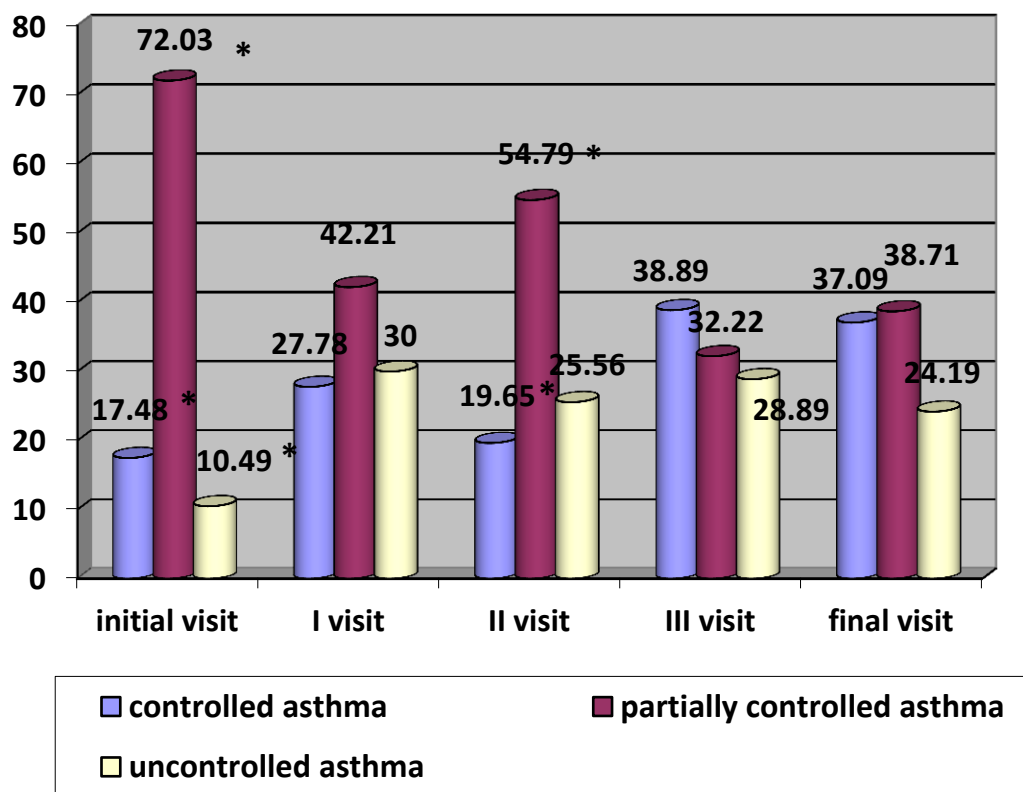
Note: * - P<0.05 relative to the final visit

Figure 1 Distribution (%) of the characteristics of asthma symptoms controllability according to the ACT questionnaire in children in the dynamics of monitoring

The distribution of characteristics of bronchial asthma symptoms controllability according to the GINA questionnaire in children in the dynamics of monitoring is shown on figure 2. Therefore, when comparing the results shown in figure 1 and 2, it can be stated that the most significant differences in the dynamic assessment of asthma symptoms control were the identification of a controlled form of asthma, which we explained from the methodological differences of the used diagnostic scales. In order to clarify the assessment of control over the symptoms of the disease, we also used a modified clinical-instrumental assessment scale in the dynamics of monitoring (Boulet et al., 2002; Li et al., 2005). The results of this assessment are shown in table 2.
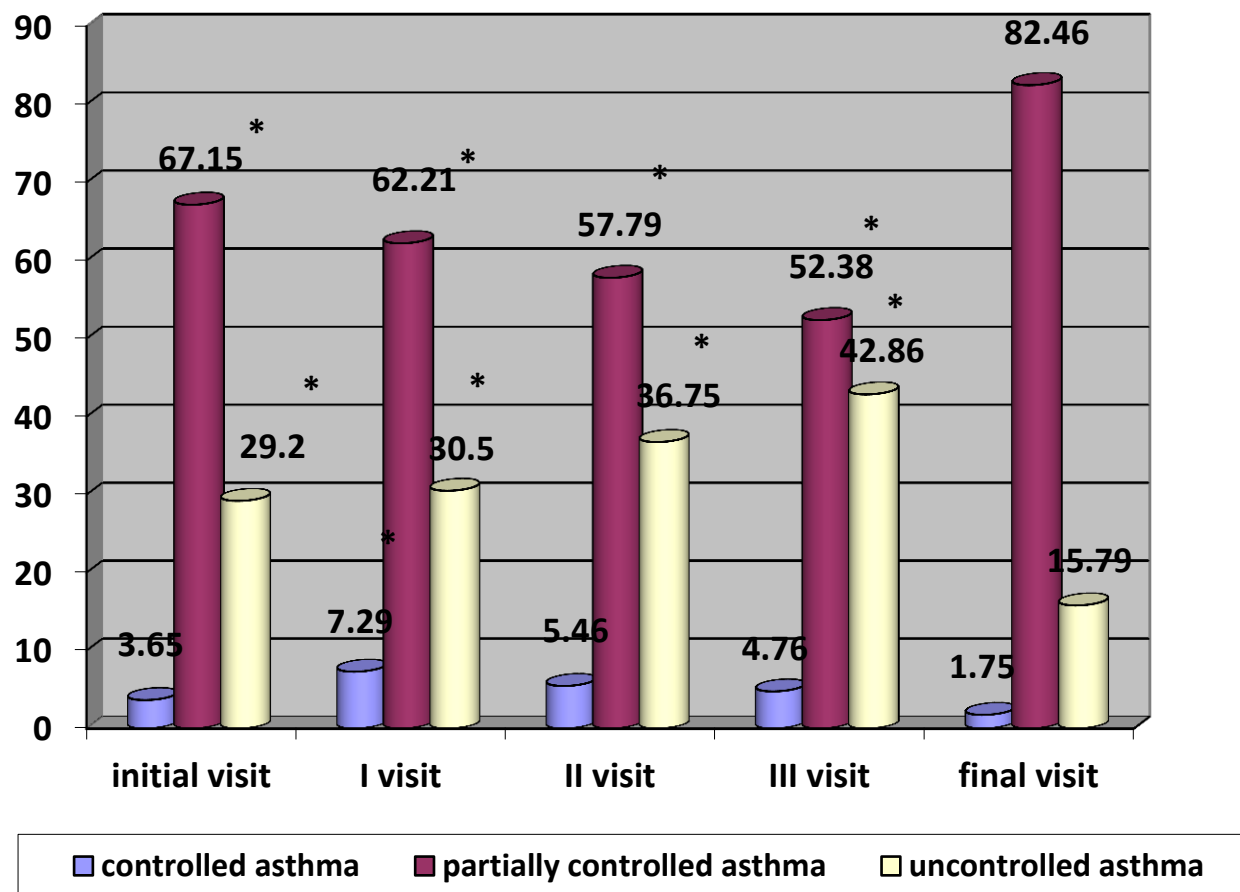
Table 2 Distribution (%) of characteristics of bronchial asthma symptoms controllability according to a clinical-instrumental scale in children in the dynamics of monitoring

Visits	Controlled asthma	Partially controlled asthma	Uncontrolled asthma
Initial visit	12.41*	39.44*	48.15*
I visit	25.32	31.65*	43.03*
II visit	18.84*	26.09*	55.07*
III visit	19.56*	28.26*	52.17*
Final visit	31.58	57.89	10.53

Note: * - P <0.05 relative to the final visit

Thus, using a modified clinical and instrumental scale in the dynamics of monitoring, a dynamic, gradual increase in the share of controlled and partially controlled asthma was determined with a statistically significant decrease in the percentage of children

with uncontrolled asthma at the final visit.

Figure 2 Distribution (%) of characteristics of bronchial asthma symptoms controllability according to the GINA questionnaire in children in the dynamics of monitoring

4. DISCUSSION

The average dose of inhaled corticosteroids (ICS) not in the exacerbation phase of asthma, established at visits, was respectively: at the first visit – 287.94 ± 14.46 mg/day, at the second – 221.36 ± 12.57 mg/day (PI: II<0.01), at III – 256.97 ± 14.38 mg/day (PII: III = 0.05), at the final – 303.70 ± 15.87 mg/day (PF: II, III <0.05). It should be noted that the reduction of the daily dose of inhaled corticosteroids at II and III visits of patients was inconsistent with estimation of the largest proportion of patients with severe asthma at the respective visits, and conversely the highest doses of corticosteroids at the initial and final visits contradicted the smallest number of children with severe persistence of the disease.

Control of asthma symptoms was determined not in the exacerbation phase during each scheduled visit of patients, as well as at the independent request of patients for counseling. The dynamic fluctuations in the distribution of qualitative characteristics of asthma symptoms control in the process of longitudinal monitoring using the ACT questionnaire allow, on the one hand, to state the effectiveness of basic anti-inflammatory therapy with a significant increase of 2.12 times the share of controlled asthma in the general cohort. However, on the other hand, with a statistical probability, the proportion of patients with low asthma control increased by 2.3 times, and the cohort of patients with partially controlled symptoms decreased by 1.9 times. An interesting fact is that the results of using the questionnaire recommended by the GINA Global Initiative did not generally coincide with the data above (GINA 2016). Thus, the share of patients with controlled asthma decreased by half, and with uncontrolled - by 1.85 times, and only the percentage of patients with partial control increased by 15.3%.

Therefore, according to the modified clinical-instrumental assessment scale at the final visit relative to the initial examination, the share of CBA increased by 2.5 times, the percentage of partially controlled bronchial asthma increased by 18.4%, and the share of uncontrolled asthma decreased by 4.6 times. In this regard, the general trends in the distribution of the nature of asthma

symptoms control, identified in the dynamics of 5-year follow-up using the GINA questionnaire and the modified clinical-instrumental assessment scale, generally coincided, except for the share of CBA (Alzahrani et al., 2016, GINA, 2016). In this respect, the results of the ACT questionnaire on trends in the frequency of CBA were associated more with the clinical-instrumental rating scale, demonstrating the effectiveness of basic anti-inflammatory treatment in dynamic longitudinal monitoring in the form of increasing the proportion of CBA by more than 2 times.

At the same time, despite the addition of clinical criteria for assessing asthma symptoms control with spirographic data in the form of a clinically instrumental scale, the dynamics of changes in the volume uncontrolled asthma probably depended on the methodology of the questionnaire, since the results of the ACT test on the GINA questionnaire and the clinical-instrumental assessment scale were deviating. However, the ACT questionnaire was the best way to predict the retention of control at the end of the 10-year dynamic follow-up period (Revicki et al., 2006; Nathan et al., 2004; Liu et al., 2007). As a test to establish in the dynamics of monitoring of cases control over asthma symptoms, the ACT questionnaire compared to the clinical-instrumental rating scale showed high specificity – 98.25% (95% CI 93.14-99.87) % and the likelihood ratio of a positive result – 21.19. With a positive test result, the post-test probability of control retention increased by 45.49%, and with a negative test decreased by 10.96%. The odds ratio of this event reached 33.1 (95% CI 7.03-105.77), attributive risk – 0.56.

As a prognostic test for loss of control over the symptoms of bronchial asthma in the survey during the final visit relative to the initial ACT test (Alzahrani et al., 2016; Revicki et al., 2006; Liu et al., 2007). when compared with the results of use for this purpose, the clinical-instrumental assessment scale had a specificity of 89.47% (95% CI 81.72-94.73)%, the likelihood of a positive result – 2.3 and the post-test probability of a positive test result increased by 19.61%, but decreased with a negative result of only by 4.13%. The ratio of the chances of losing control over the symptoms of bronchial asthma in the dynamics using the ACT questionnaire relative to the clinical-instrumental assessment scale was 2.7 (95% CI 1.24-5.95), attributive risk – 0.24.

5. CONCLUSION

During a 5-year dynamic monitoring of a cohort of school-age children diagnosed with bronchial asthma, comorbidity with allergic rhinitis increased four times, and the smallest proportion of patients were children with mild persistence of the disease while maintaining stability of patient's distribution by asthma severity. Compared to baseline data, the proportion of patients with controlled persistent bronchial asthma during the monitoring period increased statistically significantly by 2.12 times according to the ACT questionnaire and by 2.54 times according to the clinical-instrumental assessment scale. According to the GINA scale, a decrease in the proportion of such patients had no statistical probability. In the period of dynamic monitoring, the results of evaluation of the GINA questionnaire and clinical-instrumental assessment scale indicate a decrease in the proportion of uncontrolled asthma from 1.85 to 4.57 times, contrary to the ACT test, which showed an increase in the proportion of such patients by 2.3 times.

Conflict of Interest
The authors declare no conflict of interest or financial support.

Informed consent
Written & Oral informed consent was obtained from all individual participants included in the study.

Ethical approval
The study was approved by the Commission on Biomedical ethics in biomedical scientific research of the Higher State Educational Establishment of Ukraine «Bukovinian State Medical University» the protocol No. 4 dated 22 December 2020. The state registration number is 0114U002471.

Data and materials availability

All data associated with this study are present in the paper.

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