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Topical issues of step-down therapy for pediatric bronchial asthma

Key words: *Bronchial asthma, reduction of control therapy scope, children*

One of the most urgent issues of pediatric asthmology still includes matters of optimal pharmacotherapy, the purpose whereof lies in the achievement of total bronchial asthma (BA) control and prevention of its exacerbation while using minimum medications [8] with minimum therapy side effects [20]. For prevention of unwanted sequel of long-term background asthma therapy, a step-by-step approach to the therapy has been proposed, which for many years has already been the main principle of long-term control medication therapy both in adults and in children. It involves the possibility of reducing the scope of anti-inflammatory therapy (step down) upon BA control achievement and maintenance. Meanwhile, it is recommended to review the therapy every 3 months for making a decision on careful step-down reduction, depending on the disease severity [7]. Application of such approach is absolutely justified, because the step-by-step therapy scheme allows reducing the risk of long-term pharmacotherapy consequence development, as well as significantly simplifying the treatment regimen (single usage of medications during a day) and reducing its cost [10].

However in the implementation of the very principle of step-down therapy, great difficulties are caused by the diversity of BA forms and variants in children, conditioned by the severity of disease progress, age-related progress peculiarities, response to background therapy and many other factors. Especially difficult in this respect are patients with severe asthma, the scope, structure and duration of control therapy whereof varies greatly.

In spite of the fact that all of the leading consensus documents [27] recommend ICS as the medication of choice for background therapy of all persistent BA forms, leukotriene modifiers have been long ago used as an alternative medication for mild persistent asthma. As regards cromones, according to the data of many researchers [4, 5, 6], their lower clinical efficacy has been marked as compared to ICS and leukotriene antagonists [4]. Moreover, results of one meta-analysis of research of efficacy of long-term BA pediatric therapy with cromoglicid acid revealed no significant difference between cromones and placebo [34], which has been reflected in all the leading advisory documents on BA, starting from 2005 [21, 27]. Xanthine drugs, which were widely used in the past, are nowadays less popular due to a great number of side effects [27].

In case of BA control achievement and maintenance with the help of low doses of ICS in children, for instance, with persistent mild/moderate BA, possible step-down options may be:

- ICS dose reduction;
- switch to therapy with other anti-inflammatory medications – leukotriene modifiers and cromones;
- cessation of background therapy (for mild persistent BA).

However in the above clinical situation, the following options of step-down therapy are theoretically possible:

1. Reduction of daily ICS dose with preservation of their daily dosage frequency.
2. Reduction of ICS daily dosage frequency (up to 1 time per day).
3. Switch to alternating, intermittent ICS administration, when the medication is used not every day, but on certain days (every other day, several days a week).

Meanwhile, there exists no common opinion about the actual possible degree of therapy scope reduction. Reduction

of ICS dose by 25% every 3 months, as it is specified in GINA-2005, constitutes an approximate figure and has not been assessed in a sufficient number of randomized studies with children. A more advanced titration method can involve adjustment of minimum maintenance ICS dose with monitoring of nitrogen oxide (NO) concentration in inhaled air [27].

Background

In 2004, H.A. Boushey et al. [11, 13] proposed an intermitting regimen (treatment only in case of BA exacerbation) of background therapy with ICS (budesonide/prednisolone) in adult patients, based on equal, according to the author's data, clinical efficacy of periodic ICS administration and its continuous usage. At the same time, such proposal found support with pediatric specialists as well [12]. Some clinicians offered only temporary usage of intermitting regimen of ICS therapy as a step for making a decision about their full withdrawal. Others considered cessation of background therapy in case of mild persistent BA to be extremely dangerous, as patients were actually left for a certain period of time without therapy. Intermitting regimen as one of the possible approaches to background therapy scope reduction found no reflection in modern advisory documents [27].

Certainly, the necessity of selection of the minimum effective ICS dose in BA children causes no doubt. However, the possible optimal regimens of therapy scope reduction (step-down regimen), with low-dose controlled mild and moderate BA, have not yet been tried and tested and are discussed within the range of reduction from by 25% every 3 months up to complete background therapy cessation. Criteria and regimens of ICS usage frequency reduction have been understudied as well, such as, for instance, transition from double to single use in patients with optimal BA control. ICS application 1 time per day, which slightly increases patients' compliance, is allowed for some budesonide forms in BA [11]. As regards the possibility of single use of fluticasone propionate in BA, the data are controversial. Some researches demonstrate equal efficacy of double- and single-use regiments [12], while M.E. Purucker and coauthors, when analyzing the data of 9 studies dedicated to such issue, point at insufficient success of single dosing regimen [31].

Control therapy reduction at step-down stage causes unstable medically induced remission in many patients, whereupon a patient has to be again returned to the previous stage, or the therapy scope has to be increased, or the combination of medications for (step-up) background therapy has to be qualitatively changed.

Insufficient efficacy of step-down BA therapy, both in adult patients and in children, constitutes a serious problem in clinical practice. According to different authors [14, 26, 28, 30, 32], the attempt to reduce therapy scope in BA adults and children resulted in loss of disease control in 40-50% of cases.

The most often reasons for loss control at step-down BA therapy stage are:

- presence of precipitating factors:
  - undetected allergens and irritants,
  - continuation of contact with known allergens and triggers,
  - ARVI;
- presence of undetected comorbid pathology;
- lack of or inadequate therapy of diagnosed comorbid (concomitant) diseases;
- insufficient scope of anti-inflammatory background therapy;
- insufficient duration of control treatment;
- insufficient compliance with step-down therapy, including incorrect performance of inhalation technique.

It should be noted that no consensus guidelines have been developed by now that would regulate the procedure of BA step-down therapy. For instance, provisions of PRACTALL (Diagnosis and treatment of asthma in childhood, 2008) [17] consensus allow for gradual maintenance therapy reduction in case of good BA control achievement and maintenance. In such cases, it is recommended to step-by-step reduce the dose of ICS used by a patient. At the same time, it has been conclusively established that BA control achieved against the background of inhaled corticosteroids is lost as soon as elderly and pre-school patients discontinue their therapy. New demonstrative data refute the disease-modifying role of such medications in preschool children, as upon ICS withdrawal BA symptoms and exacerbation return.

In its turn, GINA (2012) [21] specifies that background therapy scope reduction is possible in case of BA control achievement in 3 and more months. In case of ICS monotherapy in medium and high doses, the medication dose should be reduced by 50% every 3 months, and in case of low doses patient should be transferred to single ICS administration per day. If BA control is achieved in case of treatment with ICS in combination with long-acting β_2-agonists (LABA), there appears a need in gradual ICS dose reduction by 50% while leaving the same LABA dose, whereupon – ICS reduction up to low dose and LABA withdrawal. Patient can be also transferred to single daily administration of a fixed combination. Another variant is also possible: LABA withdrawal at an earlier stage and transition to ICS monotherapy in the same dose, which was used in the fixed combination. However it more often results in loss of BA control. If BA control is achieved in case of ICS therapy in combination with leukotriene antagonists, it is recommended to reduce the ICS dose by 50%. Further, provided asthma control is maintained, ICS should be withdrawn with patient transfer to leukotriene antagonist monotherapy. Control therapy can be terminated in case asthma control is maintained for 1 year with the help of its minimum scope.

A slightly different approach to step-down therapy is proposed in the international advisory document on pediatric asthma - ICON (International Consensus on Pediatric Asthma, 2012) [27]. Such document contains results of critical analysis of advisory documents selected by working committee of a series of leading asthma and allergy international organizations. Among the criteria for such committee formation, there were: international participation, weight in therapeutic sphere and previous participation in writing pediatric asthma guidelines. The committee members proposed for consideration the most significant from their viewpoint documents: Australian guidelines (AAMN, 2006), guidelines of GINA (2011), GINA for children under 5 (2009), Japanese guidelines for pediatric asthma (2008), USA National guide-

lines for pediatric asthma (NAEPP, 2007), PRACTALL (2008), British guidelines for asthma therapy (SIGN, 2011). In accordance with ICON guidelines, if BA control is maintained within at least 3 months, it is allowed to reduce the therapy scope, which has to be performed gradually by titration method up to reaching the lowest effective drug dose. However, at the same time, significant variability of drug clinical efficacy in different patients is indicated, which speaks of the necessity of individual adjustment of optimal medication dose.

Japanese Guidelines for Childhood Asthma, 2011 [24] also allow for step-down therapy taking into account the severity of pediatric asthma in case of BA control maintenance within at least 3 months. If upon controller drug dose reduction up to low doses, no BA symptoms are observed and pulmonary function indicators are within normal limits, therapy can be terminated, but patient follow-up has to be performed. Meanwhile, experts indicate that currently there are no criteria for background therapy cessation.

National protocol of medical aid provision to BA children (2013) [8] admits an option of gradual reduction of intensive maintenance therapy in children with at least 3-month disease control. It is considered that transition to the step-down therapy will allow defining the minimum therapy scope required for asthma control maintenance. In case of BA control for at least 3 months in pediatrics, it is recommended to reduce the therapy scope (step down). In case of treatment with medium and high ICS doses, they are recommended to be reduced by 50%, and in case of low ICS doses it is advised to switch to single dosage regimen. In case of having reached complete control with the usage of ICS and long-acting β_2-agonist combination, it is feasible to reduce the ICS dose by 50%, while leaving the initial dose of long-acting β_2-agonists. When ICS dose used in combined therapy reaches low dose, while maintaining complete control, it is recommended to withdraw long-acting β_2-agonists. Alternatively to long-acting β_2-agonist withdrawal, it is possible to use single-administration regimen of fixed ICS and long-acting β_2-agonist combinations, or ICS monotherapy in a dose received by a child during combined therapy. Therapy with controller medications can be terminated if a patient uses low ICS doses and no symptoms are observed for 1 year.

Step-down therapy of children in their first 5 years of life involves special difficulty. It concerns both, the initial stage of asthma therapy at such age (especially in children aged 0-2) and the possibilities of therapy scope reduction and complete therapy cessation (step off) [29]. The last mentioned document is dedicated to analysis of opinions and proposals of experts from different countries of the world, set out in relevant guidelines for disease management in small children (2010) [29].

Thus, currently there are not enough scientific data on the most preferable regimen of reducing the scope of anti-inflammatory therapy in children with well-controlled BA [6], so there are no detailed guidelines for step-down BA therapy in children in any consensus paper.

At the same time, results of randomized clinical studies on the assessment of control at step-down BA therapy [23] show that each 4th patient with controlled BA, who terminated his therapy with low-dose ICS, experienced exacerbation already within the first 6 months upon their withdrawal (Figure 1). Among children with controlled asthma, who continued their therapy with low-dose ICS, the risk of BA exacerbation within the next months constituted 16%, while among the patients having terminated the ICS therapy such risk reached 38%, i.e. it was 2.4 times higher in ICS therapy cessation. Loss of asthma control was accompanied by soft decrease in pulmonary function indicators, which still required administration of short-acting β_2-agonists (SABA) in half amount as compared to the period of ICS therapy.

In 2013, a prospective 12-week study of the efficacy of BA step-down therapy was conducted in Poland with participation of 84 children aged 7-18, which investigate results of low-dose ICS substitution with montelukast [16]. BA children were monthly monitored for asthma symptoms, peak expiratory flow rate (PEF), fractional nitrogen oxide in the inhaled air (FeNO), pulmonary function indicators, sputum eosinophils and bronchial hyper-reactivity (BHR) – at the end of the study. The primary outcome measure was the number of patients that discontinued participation in the study due to BA exacerbation. 13.1% (11) of children discontinued their participation due to exacerbation. Control maintenance against the background on montelukast administration was observed in 86.9% patients. As compared to the children having discontinued their participation, the levels of sputum eosinophils and BHR in children with BA exacerbations were higher. In patients without asthma exacerbation, all the parameters, including inflammatory and BHR markers, were normal by the end of the study. A week before discontinuation of participation due to exacerbation, patients experienced aggravation of BA symptoms, increased SABA use, however no changes were observed in PEF, FEV1 and eosinophil count. Their level of sputum eosinophilia and BHR was higher than in children having finished the study, whose such indicators were normal. Researchers have arrived at a conclusion that BA control during transition from low-dose ICS to montelukast is maintained within 3 months in most children. Presence of sputum eosinophilia and BHR prior to the beginning of step-down therapy constitutes a risk factor for BA exacerbation at the stage of control therapy scope reduction.

Similar results were obtained by N. Tsurikisawa et al. (2012) [35] in the process of following up 90 percent of adult patients, who had complete BA control within 6 months against the background of ICS + LABA use and then were transferred to step-down therapy. ICS dose reduction by 50% in such patients was accompanied by loss of disease control within 6.4±3.6 months in 44% of cases. Such study also involved investigation of eosinophilic inflammation activity, which was assessed by FeNO level in the air. At the end of the study, the level of eosinophilic inflammation was analyzed in patients at the moment of therapy scope reduction. Analysis results showed that high NO levels were observed in patients with BA exacerbations at the moment of therapy scope reduction, though no clinical symptoms were recorded. Patients without BA exacerbation at the moment of step-down therapy beginning had low NO levels. Therefore, absence of clinical symptoms doesn't indicate absence of active airway inflammation. At the same time, reduction of anti-inflammatory

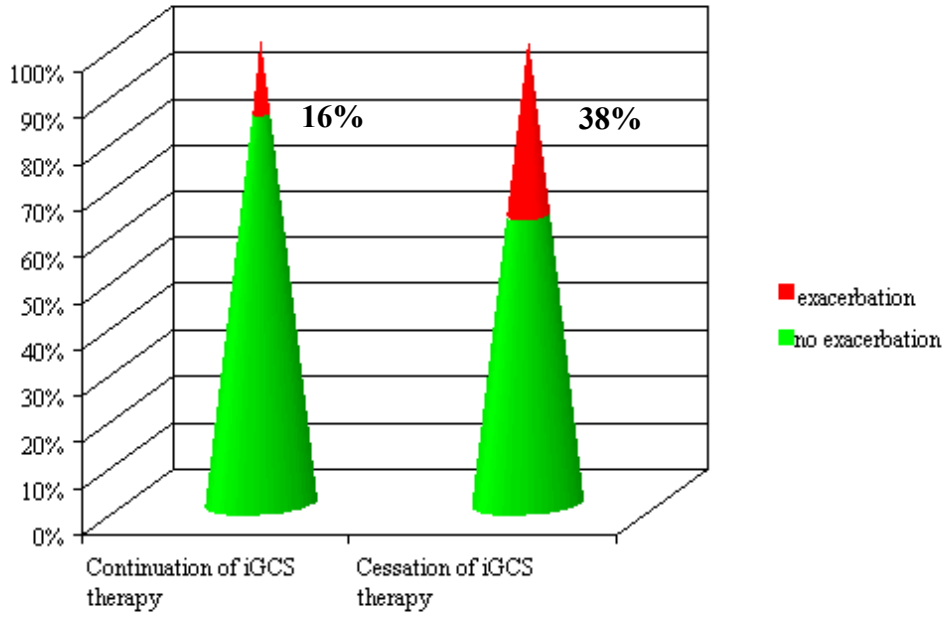

Figure 1. **Results of randomized clinical study on the assessment of bronchial asthma control in children at a step-down therapy stage (the USA, 2011) [23]**

therapy scope without account for eosinophilic inflammation intensity results in loss of clinical BA control.

On the 6th of February 2010, the U.S. Food and Drug Administration (FDA), while taking into account the results of studies having demonstrated the increase in mortality of patients receiving LABA therapy [19], and namely salmeterol (Table 1), forbade monotherapy with long-acting β_2-agonists and recommended their withdrawal as soon as asthma control is achieved.

Moreover, FDA presented results of study meta-analysis (Table 2) [36], which speak of high risk of serious consequence development in case of long-term LABA administration, such as asthma-dependent death, intubation and hospitalization, the rate whereof is much higher in BA children than in BA adults: the risk of serious case development in teenagers is 2 times higher than in adults, and the highest risk was recorded in children aged 4-11 (5.3 times higher as compared to adults and 2.7 higher as compared to teenagers).

However, according to existing guidelines, preference is given to ICS dose reduction prior to LABA withdrawal. Thus, when making a decision on their actual usage, doctors have to choose between FDA guidelines and expert opinion. FDA requested all LABA manufactures to conduct 5 randomized double blind controlled clinical studies for comparison of safety of LABA + ICS combination and ICS monotherapy. Such studies commenced in 2011. Consequences of long-term LABA usage will be assessed by FDA experts upon termination of the 6-year multinational randomized double blind prospective study that will be finished in 2017 [19]. Four out of 5 planned studies will be conducted for adults and teenagers above 12 with participation of 11,700 patients in each of them (total of 46,800 patients). Each study will investigate one of LABA-containing medications (ICS + LABA in fixed combination or each of such components in a separate inhaler). One study will be conducted for children aged 4-11 (10% of all patients) with participation of 6,200 patients. In all the studies, therapy duration will be 6 months. The primary outcome measure is planned to be the number of serious consequences: asthma-associated death, intubation and hospitalization. The children study will take into account life quality with outcome measure of number of days missed from school and asthma-caused cases of emergency actions [15, 19].

Preliminary results of such study conducted for 54 children with persistent BA controlled by a fixed ICS + LABA combination, were already published in 2012 by A.R. O'Hagan et al. [26]. The study included children with medium and severe BA with total AST-test points of over 20 and normal or close to normal spirometry indicators. Upon achievement of such parameters, there followed a switch from ICS + LABA to ICS monotherapy. Assessment of children's condition was performed every 8 weeks according to symptom control, use of emergency aid medications, including oral GCS, spirometry data, total of AST-test points, and nitrogen oxide level in exhaled air. Presence of one of the following indicators was considered to be loss of control: use of systemic GCS due to BA exacerbation, FEV1 reduction minimum by 12% and AST reduction below 20. Upon termination of 10.7 weeks, BA control was maintained in 34 (63%) children after switch to monotherapy. In 20 (37%) patients, BA control was lost, which required therapy supplementation with LTRA (montelukast) or ICS dose increase or LABA return. In 2 children, asthma exacerbation was recorded, for the treatment whereof systemic GCS were used. Patients with loss of control demonstrated significant decrease in FEV1 (-8% as compared to -1.9%, p-0.03) and AST (-3.2% as compared to -0.5%, p-0.03). Difference between NO levels in exhaled air in BA control group and loss-of-control group, was insignificant and made 23-26 ppb. On the whole, in 37% of children with medium and severe clinically controlled BA, LABA withdrawal without account for eosinophilic inflammation markers caused loss of disease control.

Table 1

Results of randomized 28-week placebo-controlled study (Salmeterol Multi-center Asthma Research Trial – SMART, 26355 patients from the age of 12) (FDA-2010) [36]

SMART patients	Asthma-related lethal cases		Risk of asthma-related death (95% CI)	Lethal cases for 10,000 (95% CI)
	Salmeterol n (% *)	Placebo n (% *)		
All patients Salmeterol: n=13176 Placebo: n = 13 179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3.13)
White patients Salmeterol: n = 9 281 Placebo: n = 9 361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1.10)
Afro-Americans Salmeterol: n = 2 366 Placebo: n = 2 319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8.46)

Table 2

Results of meta-analysis of 110 studies (60,954 patients) (FDA-2010) [36]

Patient Populations	Serious Cases		Difference in risk per 1,000 treated patients	95% CI
	LABA	non-LABA		
All patients LABA, n = 30,148 Non-LABA, n = 30,806	381	304	2.80	1.11-4.49
Patients aged 12 - 17 LABA, n = 3,103 Non-LABA, n = 3,289	48	30	5.57	0.21-10.92
Patients aged 4 - 11 LABA, n = 1,626 Non-LABA, n = 1,789	61	39	14.83	3.24-26.43

It should be noted that in 2011, the American Thoracic Society adopted an advisory document on the interpretation and usage of exhaled-air nitrogen oxide level in clinical practice. In case of presence of symptoms in children with nitrogen oxide level of 20-35 ppb, the ICS dose is recommended to be increased, and if no symptoms are observed, - it is recommended to continue ICS administration in the same dose with possible dose reduction after reaching the exhaled-air nitrogen oxide level of below 20 ppb [9].

In consideration of the foregoing, it is a fair assumption to say that clinical BA control fails to prove termination of airway inflammation activity. And namely, reduction of anti-inflammatory therapy scope and maintenance of symptomatic therapy helps achieve only clinical control of BA manifestations, while inflammatory reaction is not always properly inhibited. The higher the inflammation activity is, the more intensive is the process of airway remodeling due to inflammation persistence, which shows by increase in the number of goblet cells and vessels, hypertrophy of bronchi smooth muscle cells, submembrane collagen deposition and other unwanted consequences of structural bronchi change, which makes BA prognosis more serious.

Our clinic uses several approaches to step-down therapy in children with BA control for 3 months or for much longer (which is more often). If high ICS dose is used in ICS + LABA combination, therapy scope reduction starts from decrease of hormonal agent dose. Later, LABA and then ICS are withdrawn, and patient is transferred to monelukast sodium therapy (Singulair®) (Figure 2).

In medium ICS doses and combination of ICS + LABA + montelukast, at first ICS dose is reduced, then LABA is withdrawn, and thereupon ICS is also withdrawn with only montelukast left. If the therapy is initially based on medium doses of ICS and montelukast, step-down therapy involves gradual reduction of daily ICS dose up to their withdrawal and further child transfer to montelukast.

In case of control therapy with medium and high ICS + LABA doses, ICS dose is gradually reduced by 25-50% each month up to low ICS doses. One week prior to planned ICS withdrawal, montelukast in added, and 1-2 months later LABA is reduced by 25-50% (every 2 weeks in case of high LABA doses) up to complete LABA withdrawal, whereupon we switch to montelukast monotherapy. Each step of dose reduction and ICS and LABA withdrawal is controlled by respiratory function indicators with broncholytic test. The opinion about favorable result of adding leukotriene modifiers to ICS + LABA combination at a stage of step-down therapy is voiced also by L.Rogers and J. Reibman (2012) [33].

Addition of montelukast agent (Singulair®) at a stage of step-down BA therapy in children was substantiated by the unique mechanism of montelukast action in respect of many elements of asthma pathogenesis, which is reflected in the drug insert [1]. Thus, thanks to high selectivity and chemical affinity with cysteinyl-leukotriene receptors, it causes their significant blocking in airways. Even in low dose (5 mg), the drug ensures expressed decrease in bronchoconstriction stimulated by D4 leukotriene. Besides, its broncholytic effect develops 2 hours after oral administration, while supplementing thereby the result of β-agonist action (additive-stimulating effect). Significant clinical response is observed 2 hours after drug administration, and is maintained within 24 hours. Montelukast inhibits bronchial spasm both at the early and at the advanced stage of allergic reaction, while reducing antigen response, and reduces peripheral blood and sputum eosinophilia, which proves its apparent anti-inflammatory action. According to our data, clinical response and subjective improvement in montelukast monotherapy was recorded already on the 2nd-3rd day of drug administration in 75% of patients, which was accompanied by statistically significant improvement of respiratory function indicators and decrease in nasal secretion and induced sputum eosinophilia (after 8-week therapy – by 1.8 and 2.2 times, respectively) [3].

It should be underlined that efficacy of long-acting β2-agonists in children still remains understudied. Such drugs are absolute broncholytics, but they unfortunately provide no anti-inflammatory effect. Their long-term use can cause partial addiction both, to short- and to long-acting β_2-agonists [2], as well as unwanted consequences for patient's health [19]. Therefore, LABA drugs are not recommended for monotherapy according to GINA (2012) [21].

The difficulty of choice of the second controller drug lies in preference of drug with supplementary or anti-inflammatory or bronchodilating effect. Thus, for children with impaired pulmonary function requiring bronchodilatation, it is logical to prescribe LABA as a supplement to background ICS therapy. For patients, whose pulmonary function is normal or is insignificantly impaired, but who have symptoms of bronchial hyper-reactivity to physical exercise, cold air inhale, ARVI or allergen contact, it is feasible to prescribe montelukast as such supplement [2, 22]. Besides, it has been proven that ICS insufficiently affect leukotriene synthesis and cannot arrest their effects [18].

Continuation of anti-inflammatory therapy with montelukast at a stage of step-down therapy allows maintaining stable BA control, while simultaneously carrying out treatment of allergic rhinitis, as well as safely performing allergen-specific immunotherapy in case of respective indications.

In the end, it should be noted that the length of control treatment period corresponding to a therapy step is determined on an individual basis. Background pharmacotherapy duration quite often depends on favorable or unfavorable for a patient year season, and thus can range from 3 to 6 months or even longer. Both, at the stage of BA control maintenance and at the stage of step-down therapy, AST-test, spirometry and peakflowmetry monitoring should be considered. For assessment of active airway inflammation it is feasible to determine nitrogen oxide level in exhaled air.

Conclusions

1. Clinical BA control (absence of disease symptoms) does not exclude presence of active airway inflammation.
2. In case of active airway inflammation at the moment of step-down therapy, BA exacerbation as a rule develops within the first 3 months, which demonstrates insufficient inflammation inhibition due to inadequate duration and/or scope of anti-inflammatory therapy.

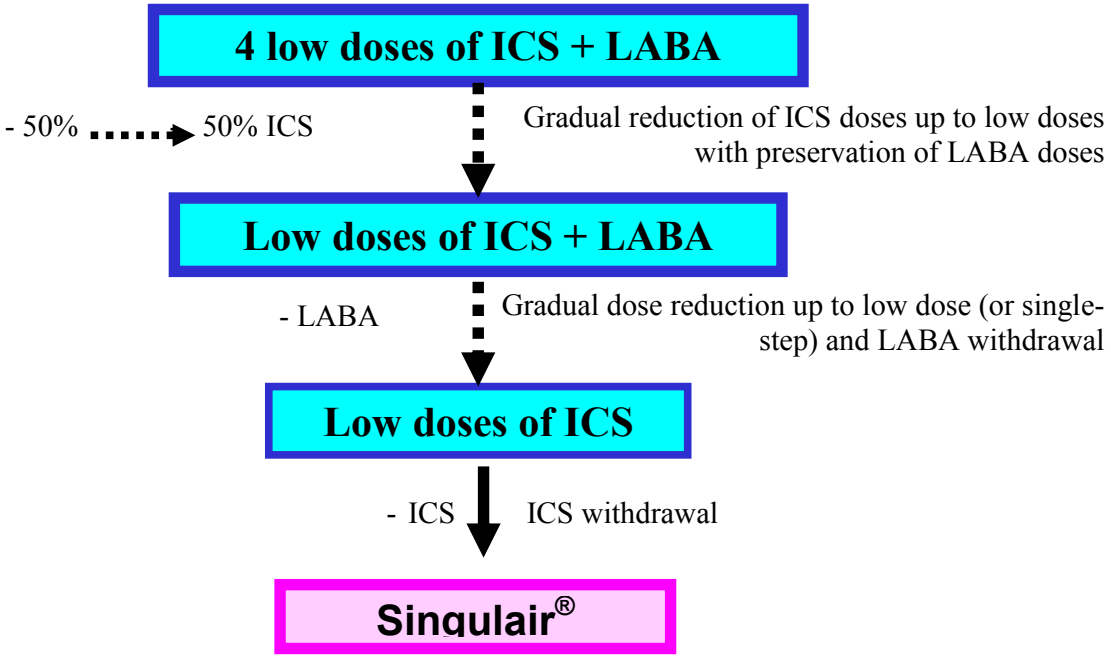

Figure 2. **Algorithm of step-down therapy in children with BA control for 3 months and more in case of high doses (4 low ICS doses) in ICS + LABA combination**

3. At the ICS -withdrawal stage of step-down therapy, it is necessary to prescribe other anti-inflammatory drugs with good risk-benefit profile.

4. Timely and pathogenetically substantiated therapy scope reduction helps to improve life quality and BA prognosis in children.

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ПРОБЛЕМНІ ПИТАННЯ «STEP DOWN» ТЕРАПІЇ БРОНХІАЛЬНОЇ АСТМИ У ДІТЕЙ

О. М. Охотнікова

Резюме

Одними з актуальних питань фармакотерапії бронхіальної астми у дітей є питання зменшення об'єму («step down») базисного (контролюючого) лікування, критерії та конкретні режими якого в наш час ще не розроблено, а тому провідні узгоджувальні документи містять лише загальні, орієнтовні рекомендації. Складність даної проблеми полягає в розмаїтті клінічних фенотипів астми в дитячому віці, а також в обмеженій можливості та небезпеці тривалого використання пролонгованих β_2-агоністів як монотерапії. У статті представлено аналіз результатів низки останніх клінічних досліджень, які стосуються ефективності збереження контролю астми на етапі «step down» терапії, з'ясуванню причин втрати контролю, пошуку шляхів і механізмів її проведення. Наведено докази недоцільності зменшення об'єму базової терапії за рахунок відміни протизапальних препаратів, зокрема інгаляційних кортикостероїдів, припинення використання яких зумовлює розвиток загострень астми вже у перші 6 місяців у 40–50 % хворих. Показана доцільність проведення моніторингу показників функції легень та рівня оксиду азоту у видихуваному повітрі при прийнятті рішення про чергове зниження об'єму контролюючої терапії. Обгрунтовано перспективність застосування модифікаторів лейкотрієнів у забезпеченні або посиленні протизапального лікування для збереження контролю. Представлено власні погляди і досвід автора щодо проведення «step down» терапії в різних клінічних ситуаціях.

Ключові слова: *бронхіальна астма, зменшення об'єму контролюючої терапії, діти.*

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TOPICAL ISSUES OF STEP-DOWN THERAPY FOR PEDIATRIC BRONCHIAL ASTHMA

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Summary

One of the pressing issues of pharmacotherapy of bronchial asthma in children is the issue of reducing («step-down») basic (cotrolling) therapy, as its criteria and specific conditions are not currently developed yet. Therefore the main supportive documents contain only general guidelines and recommendations. The complication of the issue lies in variety of clinical phenotypes of asthma in infancy as well as in limited opportunities and danger of prolonged use of prolonged β_2-agonists as monotherapy. The article presents the analysis of number of recent clinical studies relating to the efficiency of maintenance of asthma control on the stage of «step-down» therapy, identification of the causes of loss of control, the finding of the ways and mechanisms of its performance. It was proved that reduction of basic therapy by withdrawing anti-inflammatory drugs, inhalation corticosteroids in particular, is not appropriate. Discontinuation of the latter leads to asthma acute attacks development in the first 6 months in 40–50 % of patients. It is suggested to monitor indicators of respiratory function and levels of nitric oxide in exhaled air which is very rational in making decision about the next controlling therapy decline. The prospects of leukotriene modifiers use in providing or enhancing anti-inflammatory therapy to maintain control are affirmed. The author's personal opinions and experience of performing «step-down» therapy in various clinical situations are presented.

Key words: *bronchial asthma, decrease of controlling therapy, children.*

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