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The statement of the Polish Society of Allergology experts on the treatment of difficult-to-treat asthma

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Abstract

The main objective of asthma treatment is to control symptoms of the disease; however, despite the availability of guidelines and many groups of medications, the degree of control of this condition is insufficient. In difficult-to-treat asthma, the optimal control cannot be achieved due to reasons independent of the disease. Factors worsening asthma control include: inadequate treatment plan (low therapy adherence and compliance), inappropriate inhalation technique, insufficient symptom control using the available classes of medications, incomplete response to treatment (non-responders, steroid-resistance), incorrect diagnosis of asthma or comorbidities, and environmental factors. In order to achieve the optimal asthma control, it is recommended to: take therapeutic decisions with the patient, assess the probability of non-compliance, perform detailed diagnostics and initiate treatment of concomitant diseases, carry out differential diagnosis of conditions mimicking asthma, educate the patient as to the inhalation technique and check it, eliminate unfavourable environmental factors, and modify current treatment. New treatment options for patients with asthma include: ultra-long-acting beta2-agonists, long-acting muscarine receptor antagonists (LAMA), monoclonal antibodies, and non-pharmacological interventions. The only LAMA approved for treatment of asthma is tiotropium bromide. The analyses performed demonstrated a high efficacy of tiotropium in terms of improved lung function parameters and prolonged time to the first asthma exacerbation. It is recommended as an add-on therapy at asthma treatment steps 4 and 5 according to GINA (Global Initiative for Asthma) 2014. The optimal asthma control is important from the medical as well as the economical point of view.

Key words: asthma, bronchodilators, asthma control, difficult-to-treat asthma

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Definition

Asthma is a chronic inflammatory disease of the lower airways, characterised by episodes of dyspnoea, cough, and chest discomfort. The main objective of asthma treatment is to control symptoms, prevent exacerbations, and inhibit deterioration of lung function, while maintaining the optimal safety profile of the applied interventions. Despite guidelines developed and continuously improved by expert groups, the degree of asthma control remains insufficient in many countries [1].

Difficult-to-treat asthma is defined as asthma in which control cannot be achieved due to reasons independent of the disease (such as co-morbidities, exposure to environmental factors, or non-compliance) [2].

Severe asthma is diagnosed when the optimal symptom control has not been achieved despite

compliance, the use of high-doses of ICS in combination with other agents, and adequate control or the lack of concomitant diseases. This category includes also patients in whom an attempt to introduce less aggressive treatment results in worsening of asthma control [2].

In order to define precisely the subgroups of patients with different reactions to treatment, the following terms must be distinguished: severe asthma, uncontrolled asthma, difficult-to-treat asthma, and refractory asthma.

According to the ATS/ERS criteria, severe asthma is defined as follows [3, 4]:
— in order to prevent asthma from being uncontrolled, GINA step 4 or 5 treatment (i.e. high-dose inhaled glucocorticosteroids [ICS] and long-acting beta-2-agonists [LABA] + other controllers) has been required in the previous year, or systemic glucocorticosteroids have been used in more than 50% of days of the year, or
— despite such treatment, the optimal control has not been achieved.

Epidemiology of uncontrolled asthma

The available epidemiological data suggest that in about 5–10% of adult patients, the optimal asthma control is not achieved, even if GINA 2015 step 4 or 5 treatment is applied [5]. Asthma control according to GINA is difficult to estimate as it is based on the patient's subjective assessment, affected by gradual adaptation to symptoms, increasing with time and clinical progression of the disease. In an international study evaluating the degree of asthma control in Central and Eastern Europe (Asthma Insights & Reality in Central and Eastern Europe — AIRCEE), a group of 300 Polish patients with asthma was investigated [6]. More than 70% of respondents reported the occurrence of asthma symptoms at least once a week, and in 20% symptoms were present on every day. In the investigated group, 45% of patients complained of symptoms at night, of whom in 11% the symptoms were present every night. More than 50% of patients required the use of on-demand bronchodilators. Only 27% of patients with asthma used ICS. In the investigated group, 18% of adult patients and 8% of children were hospitalized, and nearly half of the patients had required emergency room treatment due to asthma in the previous year.

Asthma control criteria

According to the criteria proposed by ERS/ATS [3, 4], asthma is uncontrolled when at least one of the following is true , despite GINA step 4 or 5 treatment or systemic CS for more than half of the previous year:
— insufficient symptom control, i.e. the Asthma Control Questionnaire score consistently over 1.5, or the Asthma Control Test score below 20;
— frequent severe exacerbations, i.e. two or more episodes requiring systemic glucocorticosteroids (lasting more than 3 days) in the previous year;
— serious exacerbations, i.e. at least one hospitalization, stay at an intensive care unit, or mechanical ventilation in the previous year;
— airflow limitation, i.e. post-bronchodilator FEV_1 below 80% of the predicted value;
— controlled asthma that worsens on tapering of high doses of ICS or systemic glucocorticosteroids.

Experts' recommendation

The degree of asthma control should be assessed in two domains, i.e. current symptom control and the risk of future events (exacerbations, deterioration of lung function, or respiratory disability). Airflow limitation should be monitored by means of assessment of lung function: before treatment initiation or modification, after 3–6 months, and periodically during the treatment (at least once a year).

Asthma severity should be first assessed after several months of treatment. According to GINA 2014, uncontrolled asthma should be diagnosed when at least 3 of the following criteria are met [2]: symptoms of the disease are present more than twice a week; nocturnal awaking occurs; rescue inhalers (apart from preventive application before exercise) are used more than twice a week; limitation of everyday activities is present.

If the optimal asthma control has not been achieved, the following actions should be undertaken in parallel:
— correctness of the inhalation technique should be checked and the patient should be adequately trained or the method of application of inhaled medications should be changed;
— differential diagnostics of conditions with a clinical picture that may be similar to that of asthma should be carried out;
— the diagnosis of asthma should be confirmed;
— concomitant diseases should be effectively treated;
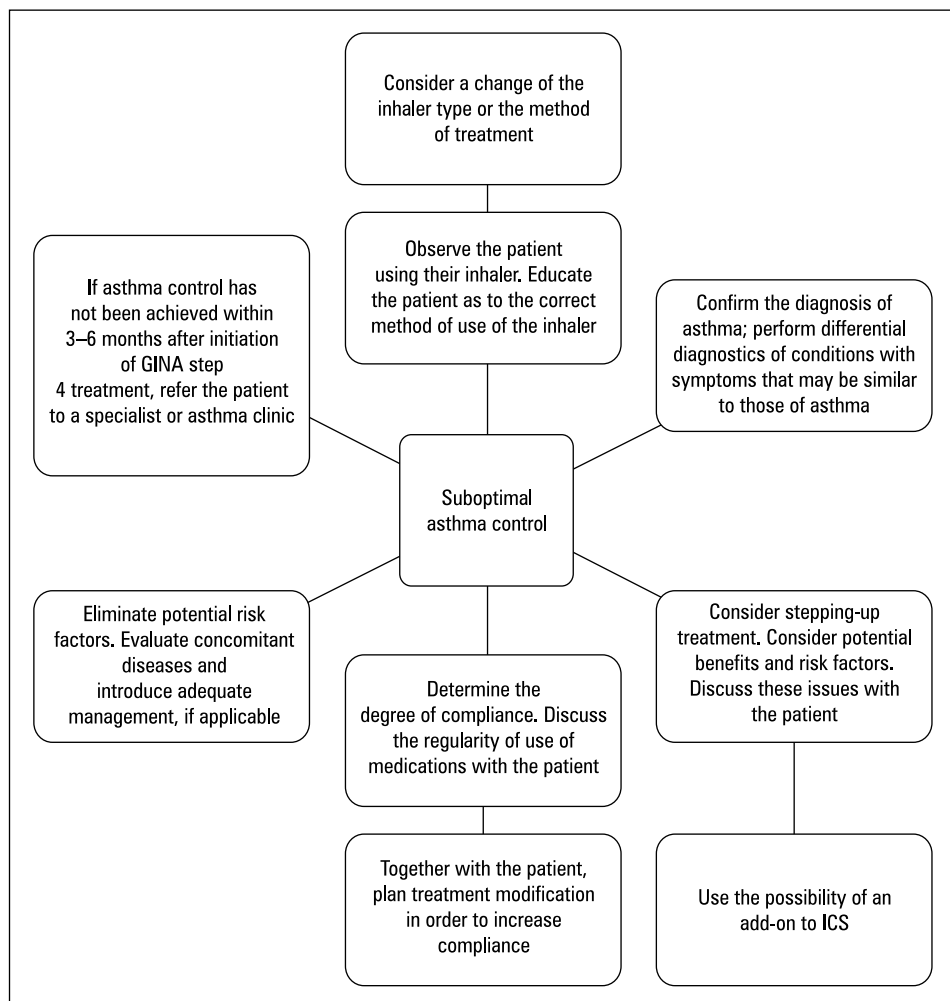— unfavorable environmental factors should be eliminated, if possible;

Figure 1. Recommended management of patients with suboptimal asthma control

— the treatment plan should be adjusted to the patient's needs, any doubts should be discussed, and further treatment should be planned with the patient;
— introduction of additional medications or stepping-up of treatment (according to GINA 2015) should be considered.

Diagnosing and monitoring of factors affecting asthma control

The most important factors impairing asthma control include:
— low therapy adherence and compliance (i.e. inadequate treatment plan) [7, 8],
— incorrect inhalation technique [8],
— insufficient symptom control using the available classes of medications [9, 10],
— incomplete response to treatment (non-responders, steroid-resistance),
— incorrect diagnosis of asthma or comorbidities,
— environmental factors [11, 12].

In case of asthma treatment failure, the authors recommend an algorithm presented on Figure 1.

Low patient's compliance and adherence to treatment

One problem impairing achievement of the optimal asthma control is patient non-compliance. The term "compliance" refers to the degree to which a patient correctly follows medical advice. At present, a wider term "adherence" is used more commonly; this includes and stresses the patient's active participation in treatment planning and implementation of the developed treatment plan. It is estimated that about 50% of adults and children receiving long-term treatment due to asthma do not use their medication in the correct manner [13]. What is important, this happens more often in patients with difficult-to-treat asthma than in patients with well-controlled asthma, and there-

fore achievement of satisfactory treatment effects is extremely difficult. Apparently, in everyday practice this may be one of the main reasons for the lack of optimal asthma control. In a British study, 35% of patients with asthma prescribed with inhaled combination treatment complied with the medical advice in less than 50% [14]. In another study, 65% of patients using ICS and 60% of those using long-acting β2-agonists complied with the medical advice in less than 80% [15]. Low-adherence patients had significantly worse lung function parameters (post-bronchodilator FEV_1 75.4 vs. 84.3, p < 0.05), higher probability of ventilation disorders due to asthma (19.2% vs. 2.6%, p = 0.02), and higher sputum eosinophil counts (0.66% vs. 0.54%, p = 0.05) [16].

Reasons for insufficient treatment adherence include [2]:
1. Treatment regimen (difficulties using the inhaler; multiple inhalations per day; use of several different inhalers).
2. Unintentional factors (misunderstanding of the instructions; forgetfulness; absence of a daily routine; treatment cost).
3. Intentional factors (perception that treatment is not necessary; denial or anger about asthma or its treatment; inappropriate expectations; concerns about adverse effects (mainly steroidophobia); dissatisfaction with health care providers; stigmatization; cultural or religious issues; treatment cost).

In assessment and improvement of adherence, the skill of appropriate conversation with asthma patients is important. Asking the right questions is an important issue; for example [17]: "Many patients do not use their inhaler as prescribed. In the last month, how many days per week have you used your prescribed inhalers — not at all, once, twice, three times, or more?" or "Do you find it easier to remember to use your inhaler in the morning or in the evening?" In Poland, it is also possible to check the date of the last prescription of inhalers for a specific patient and the date and dose counter on the inhaler.

> **Experts' recommendation**
>
> In order to achieve the optimal adherence, it is recommended to take the decision on selection of the optimal treatment option with the patient [18]. Modification of ICS dosing is worth considering (according to study results, one dose per day instead of two improves adherence[19]). During follow-up visits, the probability of non-adherence should be assessed, and the patient should be encouraged to discuss optimization of the applied treatment.

Comorbidities and diseases with clinical picture similar to that of asthma

One reason for poor asthma control is inadequate treatment or the lack of treatment of concomitant diseases. Comorbidities are recognized as a factor increasing the risk of asthma exacerbations [20]. In patients with asthma, conditions such as gastroesophageal reflux, obesity, obstructive sleep apnoea, or chronic rhinitis and sinusitis are common and require diagnostics and specialist treatment. Psychological problems that should be consulted with a psychologist or a psychiatrist are also quite common.

If asthma control is difficult to achieve, differential diagnostics of conditions with symptoms that may be similar to those of asthma should be intensified. According to data, in 12–30% of cases "uncontrolled asthma" was actually another, misdiagnosed condition [21, 22]. The most common conditions that may be mistaken for asthma and their differential diagnosis are presented in Table 1.

> **Experts' recommendation**
>
> If asthma control is difficult to achieve, detailed differential diagnostics of conditions with symptoms that may be similar to those of asthma and/or concomitant diseases impairing achievement of the optimal asthma control should be performed.

Incorrect inhalation technique

Incorrect inhalation technique is a factor impairing achievement of the optimal asthma control as it increases the risk of both disease exacerbations and the adverse effects of treatment [23]. It is estimated that most patients (up to 70–80%) use their inhalers in an incorrect manner and are not aware of the errors they make. In a French survey study, 3955 patients with asthma using ICS delivered via a pressurized metered dose inhaler took part [24]. Incorrect use of the inhaler was observed in 71% of the participants, of whom 47% used it incorrectly due to poor coordination between inspiration and dose release. In the same group, 78% of the respondents made more than 1 error or omission during an inhalation. Despite that, only 15% of patients who used their inhalers incorrectly and 23% of those with poor coordination reported their inhalation technique as poor or very poor. It is worth stressing that some physicians are not able to demonstrate the correct method of use of the inhaler they prescribe to the patient [25].

Table 1. Asthma differential diagnoses in adult patients

Disease	Diagnostics
Vocal cord dysfunction	Laryngoscopy/plethysmography
Diseases of the paranasal sinuses	Computed tomography, endoscopy
Obstructive sleep apnoea	Polysomnography
COPD	Thorough medical history, spirometry
Bronchiolitis obliterans	Plethysmography/HRCT/biopsy with histopathological examination
Hyperventilation in anxiety episodes	Consultation by a psychiatrist
Interstitial lung diseases	Lung diffusion capacity test/chest HRCT
Bronchiectases	Chest HRCT
Emphysema	Lung diffusion capacity test/chest HRCT
Pulmonary embolism	Chest angio-CT
Foreign body in the airways (aspiration, tumour, others)	Bronchoscopy
Gastrooesophageal reflux disease (GERD)	Gastroscopy/pH-metry
Churg-Strauss Syndrome	Biopsy with histopathological examination, ANCA
Cystic fibrosis	Sweat test
Adverse effects of angiotensin converting enzyme inhibitors	Medical history
Congestive heart failure	Echocardiography/BNP
Allergic bronchopulmonary aspergillosis	Chest HRCT, sputum examination for mould filaments, skin tests, cIgE, sIgE, precipitins
Sarcoidosis	Imaging tests, biopsy with histopathological examination
Pulmonary hypertension	Angio-CT of pulmonary arteries, vessel catheterization, heart ultrasound

Education is a factor that may significantly improve the patients' inhalation technique. Guidance as to the use of the inhaler was provided to 84% of the respondents, and in 68% of them correctness of the inhalation technique was checked and possible errors corrected [264]. The patients who received training in both aspects mentioned above made significantly less errors using their inhalers (66.5% vs. 86.4%; p < 0.0001). The patients who received no instructions were more likely to report due to exacerbation of asthma symptoms than those trained by the physician (3.3% vs. 6.2%; p = 0.005). A slight but statistically significant decrease of the peak expiratory flow rate was also noted in patients who were not instructed as to the inhalation technique in comparison with patients who received such instructions (70.4 ± 0.4 vs. 72.9 ± 1.0; p = 0.02).

Experts' recommendation

When prescribing inhaled medications for the first time, it is recommended to instruct the patient as to the use of the inhaler and the inhalation technique, and to check correctness of the inhalation technique during follow-up visits. The first step is selection of the appropriate inhaler type. The availability of specific types, their price, and the convenience of application should be taken into account. It is recommended that the patient should take part in decision-making for the method of administration of inhaled medications. In the case of pressurized metered dose inhalers, the use of a spacer improves deposition of drug particles and reduces the risk of adverse effects (for ICS — oral candidiasis, dysphonia). It is also important to determine whether any conditions or physical barriers potentially affecting the process of inhalation are present. If multiple inhaled medications are prescribed, it is beneficial to prescribe them in the same inhaler. If the patient has problems to learn an effective inhalation technique, an alternative method of administration of inhaled medications may be considered. It is recommended to avoid frequent changes of the inhaler type and the use of multiple different inhalers in the same patient.

New treatment options

Limited efficacy of medications currently used in the treatment of severe asthma makes it necessary to look for new treatment options.

Table 2. Add-on therapies in the non-controlled asthma treatment according to GINA 2014 and ERS/ATS, modified

Group	Type	Efficacy
Without phenotyping	Tiotropium	Recently approved for treatment of asthma in the European Union. Efficacy in lung function improvement, symptom reduction, and control of disease exacerbations
	Theophylline	No effect on the number of asthma exacerbations despite improved results of lung function tests
	LTRA	Efficacy in lung function improvement and control of disease exacerbations; less common adverse effects in comparison with LABA but worse compliance
	Low doses of oral glucocortico-steroids	Benefits and risks associated with adverse effects must be thoroughly considered in each case
With phenotyping	Anti-IgE therapy (omalizumab)	ICS dose reduction and decreased frequency of asthma exacerbations with an acceptable safety profile
	Sputum-based ICS dose optimisation	Effective in reduction of frequency of asthma exacerbations in selected patients
	Anti-IL-5 therapy (mepolizumab)	Improved asthma control, reduction of exacerbations
	Anti-IL-13 therapy (lebrikizumab)	Improvement of lung function parameters, reduction of frequency of asthma exacerbations. Phase 2 of clinical trials has recently been completed.
	Anti-IL-4 and anti-IL-13 therapy (dupilumab)	Reduction of frequency of exacerbations in moderate to severe asthma
	CXCR2 antagonists	Currently in the stage of initial trials
Non-pharmacological interventions	Bronchial thermoplasty	Efficacy in certain patient groups. No data on long-term effects

At present, new classes of medications, including ultra-long-acting beta2-agonists (uLABA) and long-acting muscarine receptor antagonists (LAMA) are being intensively investigated.

Long-acting muscarine receptor antagonists (LAMA) constitute a group of bronchodilators with a mechanism of action different from that of LABA. These are anticholinergic agents, mainly antagonists of the M3 receptor present in bronchial smooth muscles, that act to relax them. This group includes such compounds as tiotropium, aclidinium, umeclidinium, and glycopyrronium. At present, the only marketed agent in this group registered for asthma treatment is tiotropium bromide. This agent will be discussed in more detail below in this review.

Apparently, in order to improve compliance, future treatment of moderate to severe asthma will be based on combination products containing two or three medications (ICS, uLABA, and/or LAMA) in one inhaler.

New biological treatments (other than omalizumab) are not discussed in detail as their efficacy and safety profiles are being investigated. The only agent in this group registered for asthma treatment is omalizumab — an anti-IgE antibody. GINA 2014 guidelines recommend its use in patients with moderate to severe asthma in whom the optimal asthma control cannot be achieved using step 4 treatment [2]. In most cases, it is well tolerated; adverse effects typical for biologic treatments (including anaphylactic reactions) may occur sporadically. A disadvantage of biologic therapies is a high treatment cost. The incremental cost-effectiveness ratio for omalizumab is GBP 83,822 per quality-adjusted life year (QALY) in adults and adolescents [27].

New add-on treatment options are summarized in Table 2.

Another option is the use of uLABA. Their mechanism of action is the same as that of conventional LABA. The activity of the currently used LABA (i.e. salmeterol and formoterol) lasts 12 hours which makes it necessary to use them in at least 2 daily doses. New uLABA remain active for more than 24 hours. This group includes olodaterol, indacaterol, and vilanterol. Indacaterol is an uLABA registered for use in treatment of patients with COPD in the USA and Europe. The results of a randomised, double-blind clinical trial demonstrated that indacaterol in combination with mometasone furoate was at least as efficacious as mometasone with respect to the time to the first serious asthma exacerbation (0.3% vs. 0.8%; p = 0.16) [28]. A combination of indacaterol and mometasone was superior to mometasone

alone with respect to the total number of asthma exacerbations requiring oral glucocorticosteroids per year (rate ratio: 0.71; 95% CI: 0.55 to 0.90; p = 0.005). The number of patients in whom adverse effects occurred was similar in both groups. Vilanterol is available in combination with fluticasone furoate and has been registered by the European Medicines Agency (EMA) for treatment of both COPD and asthma. The use of this product in the diseases mentioned above is justified by the results of randomised clinical trials that demonstrated the efficacy of vilanterol in patients with asthma [29]. In a randomised clinical trial, the participants (n = 2020) were assigned to one of two groups [30]. In one group, the patients received one dose of vilanterol (22 mcg) in combination with fluticasone (92 mcg), and in the other — one daily dose of fluticasone (92 mcg). The patients receiving vilanterol gained additional benefit from treatment in comparison with those receiving ICS only — a significant reduction of the probability of a severe asthma exacerbation in 52 weeks (from 15.9% to 12.8%; p = 0.036) was demonstrated. A study by Woodcock et al. in a large group of patients (n = 806) demonstrated no statistically significant differences with respect to most endpoints concerning lung function tests between patients receiving fluticasone furoate (92 mcg) and vilanterol (22 mcg) in a single daily dose and those using fluticasone propionate (250 mcg) and salmeterol (50 mcg) twice daily [31]. In a post hoc analysis, a significant improvement of the quality of life measured using the AQLQ+12 questionnaire (scores higher by ≥ 0.5) in favour of the combination of fluticasone furoate and vilanterol (OR = 1.39 [1.02; 1.89]).

Role of tiotropium in asthma control

Tiotropium bromide is a muscarine receptor antagonist, i.e. an anticholinergic agent. Although it is not selective for specific subtypes of the muscarine receptor, after topical application it acts mainly as an antagonist of the M3 receptor, present on smooth muscle cells and the cells of submucosal glands [32]. Its activity results in smooth muscle relaxation and decreased mucus production, and eventually in bronchodilation. Tiotropium remains active for more than 24 hours and therefore may be applied in a single daily dose [33].

So far, tiotropium delivered by the Handi-Haler® or Respimat® inhaler, has been registered for use in treatment of COPD, in which numerous clinical trials made it possible to investigate thoroughly the activity and safety profile of this agent. The analyses demonstrated a significant effect of tiotropium on lung function parameters and subjective reduction of dyspnoea in patients with COPD [34, 35].

In the search of new treatment options for patients with asthma (for whom, except an anti-IgE monoclonal antibody, no new groups of medications have been registered for more than 10 years), investigators focused on long-acting anticholinergic agents, including tiotropium. In the TALC (Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid) study, the efficacy of tiotropium added to ICS in patients with uncontrolled asthma receiving ICS alone was evaluated [36]. One tested hypothesis was that in patients with asthma suboptimally controlled with ICS alone, the addition of tiotropium bromide would be more beneficial than doubling the dose of ICS. Another hypothesis was that in such patients the addition of tiotropium would be no less efficacious than the addition of a LABA. The study inclusion criteria were: age over 18 years, a history of asthma confirmed by bronchial obstruction reversibility test or bronchial hyper-reactivity, FEV_1 higher than 40%, and non-smoking status (less than 10 pack years). The primary endpoint was PEF measured in the morning. Secondary endpoints included: pre-bronchodilator FEV_1, the number of days with optimal asthma control (defined as days without symptoms, on which the use of emergency bronchodilators was not necessary), symptoms of the disease, the use of emergency bronchodilators, asthma exacerbations (defined as increased severity of asthma symptoms requiring the use of oral glucocorticosteroids, or increased dose of ICS or other asthma medications), the utilisation of healthcare services, respiratory inflammation markers, and validated questionnaires concerning the course and treatment of asthma (Asthma Control Questionnaire, Asthma Symptom Utility Index, Asthma Quality-of-Life Questionnaire). Two hundred and ten patients with moderate chronic asthma in whom disease control was not achieved with inhaled beclomethasone (80 mcg twice daily) were randomized into three groups: addition of tiotropium (18 mcg) to beclomethasone, along with a salmeterol inhaler containing placebo; doubled dose of beclomethasone (160 mcg) in two daily doses with addition of a salmeterol inhaler containing placebo and a tiotropium inhaler containing placebo; addition of salmeterol (50 mcg twice daily) to beclomethasone, along

with a tiotropium inhaler containing placebo. In patients receiving tiotropium, the morning PEF was significantly higher (by 25.8 litres per minute) than in patients receiving a double dose of the ICS (95% CI: 14.4 to 27.1; p < 0.001). Similar results were obtained for the comparison of patients receiving tiotropium with those receiving the doubled dose of ICS with respect to evening PEF values (a difference of 35.5 litres in favour of tiotropium; 95% CI: 24.6 to 46.0; p < 0.001), pre-bronchodilator FEV_1 (a difference of 0.1 litres in favour of tiotropium; 95% CI: 0.03 to 0.17; p = 0.0004), the proportion of days with optimal asthma control (a difference of 0.079 in favour of tiotropium; 95% CI: 0.019 to 0.14; p = 0.01), assessment of daily asthma symptoms (a difference of −0.11 in favour of tiotropium; 95% CI: −0.16 to −0.06; p < 0.001), the Asthma Control Questionnaire score (a difference of −0.18 in favour of tiotropium; 95% CI: −0.34 to −0.03; p = 0.02), and FEV_1 after 4 inhaled doses of albuterol (a difference of −0.04 liter in favour of tiotropium; 95% CI: 0.01 to 0.008; p = 0.01). In comparison with patients receiving salmeterol, no differences were found in patients using tiotropium with respect to morning or evening PEF values, the proportion of days with optimal asthma control, assessment of daily asthma symptoms, or the Asthma Control Questionnaire score. Greater benefits from addition of tiotropium in comparison with salmeterol as an add-on to ICS therapy were observed with respect to pre-bronchodilator FEV_1 (a difference of 0.11 liter in favor of tiotropium; 95% CI: 0.04 to 0.18; p = 0.003) and FEV_1 after 4 inhaled doses of albuterol (an increase of 0.07 liter in favour of tiotropium; 95% CI: 0.05 to 0.010; p < 0.001).

In two randomized clinical trials, 912 patients with severe asthma were analyzed. They were randomized to two groups: in one, tiotropium 5 mcg delivered via the Respimat inhaler was added to the background therapy; in the other, the patients received placebo [37]. Enrolled patients were those with severe asthma in whom the disease remained uncontrolled despite treatment with ICS and LABA, with objective signs of chronic obstruction (post-bronchodilator FEV_1 ≤ 80%). In week 24, in patients receiving tiotropium a significant improvement of the FEV_1 values in 24-hour monitoring and of the mean weekly morning PEF values were observed. Addition of tiotropium significantly prolonged the time to the first severe exacerbation by 56 days in comparison with the placebo group (an improvement by 31%) and reduced the risk of exacerbation by 21% in comparison with the control group (relative risk 0.79; p = 0.03). The effect of added tiotropium on the time to subsequent exacerbations was not investigated. In addition, tiotropium was found to have a favorable safety profile – its addition was not associated with more adverse effects than in the placebo group.

An analysis of ACQ-7 (Asthma Control Questionnaire) forms from 6 phase III randomized clinical trials in patients with symptomatic asthma demonstrated a significant improvement with respect to asthma symptom reduction following addition of tiotropium bromide to standard treatment (i.e. at least ICS) [38]. The analysis included: two 48-week clinical trials (PrimoTinA — addition of tiotropium 5 mcg to ICS), two 24-week clinical trials (MezzoTinA — addition of tiotropium 5/2.5 mcg to ICS), a 12-week clinical trial (GraziaTinA — addition of tiotropium 5/2.5 mcg to ICS), and a 52-week clinical trial (Study 464 — addition of tiotropium 5/2.5 mcg to ICS). The respective mean basic ACQ-7 scores were: PrimoTinA 2.63 (SD 0.69); MezzoTinA 2.18 (SD 0.49); GraziaTinA 2.10 (SD 0.42); Study 464 1.95 (SD 0.39). The mean difference with respect to response in favor of tiotropium for specific studies was: PrimoTinA, 5 mcg −0.132 ± 0.049 (p = 0.007); MezzoTinA, 5 mcg −0.115 ± 0.043 (p = 0.008), 2.5 mcg −0.160 ± 0.043 (p < 0.001); GraziaTinA, 5 mcg 0.014 ± 0.067 (p = 0.835), 2.5 mcg 0.061 ± 0.067 (p = 0.362). The mean ACQ-7 score in the Study 464 was 0.98 (SD 0.63), 1.09 (SD 0.72), and 0.99 (SD 0.68) for 5 mcg, 2.5 mcg, and placebo, respectively. The study demonstrated that the addition of tiotropium bromide in a single daily dose to ICS therapy was associated with improved asthma control.

An advantage of tiotropium is its convenient dosing — the administration of one daily dose of 5 mcg makes it possible to achieve the same lung function parameters as with two doses of 2.5 mcg [33].

The asthma/COPD overlap syndrome (ACOS) in which asthma coexists with chronic obstructive pulmonary disease (COPD) is commonly encountered in clinical practice. The definitions, diagnostic methods, and potential practical importance of the diagnosis of ACOS require further research and discussion. In general practice, it is sometimes difficult to establish an unequivocal diagnosis, and addition of tiotropium is beneficial in both conditions. Magnussen et al. published the results of a randomized clinical trial evaluating the efficacy of addition of tiotropium to standard treatment in patients suffering from both

Table 3. The proposed role of LAMA (tiotropium) in the asthma treatment in adults as *add-on* to the GINA 2014 recommendations

Step	Background treatment		Rescue medications	Other recommended interventions
	First-line	**Alternative**		
1	No treatment	Low-dose ICS	SABA	Treatment of concomitant diseases. Patient education. Inhalation technique control. Avoidance of the risk factors of exacerbations. Non-pharmacological interventions (e.g. specific immunotherapy).
2	Low-dose ICS	Low-dose theophylline/LTRA		
3	Low-dose ICS + LABA	Medium- or high-dose ICS or low-dose ICS + LTRA/**tiotropium**	SABA or low-dose ICS + formoterol in one inhaler	
4	Medium- or high-dose ICS + LABA + **tiotropium** (possibly)	Medium- or high-dose ICS + LTRA/**tiotropium**		
5	Add-on therapy (e.g. addition of anti-IgE, bronchial thermoplasty (?), sputum testing), referral to a specialist	Low-dose oral glucocorticosteroids for a short time		

asthma and COPD [39]. Four hundred and seventy two patients were randomized to two groups. One group received conventional treatment to which tiotropium in a daily dose of 18 mcg, while the other group received conventional treatment with placebo. A significant improvement with respect to the primary endpoint, i.e. the area under the FEV_1 curve from 0 to 6 hours (a difference of 186 ± 24 ml in favor of tiotropium; $p < 0.001$) and the morning FEV_1 values before treatment administration (a difference of 98 ± 23 ml in favor of tiotropium; $p < 0.001$), was observed. Benefits from the addition of tiotropium were also visible with respect to the FVC values before treatment administration (a difference of 128 ± 34 ml; $p < 0.001$) and the area under the FVC curve from 0 to 6 hours (a difference of 232 ± 35 ml; $p < 0.001$). In comparison with the situation before treatment initiation, the mean number of salbutamol doses per week was reduced by 0.05 ± 0.12 doses per day in the placebo group and by 0.5 ± 0.12 doses per day in the tiotropium group in the 12th week of treatment ($p < 0.05$).

At present, tiotropium bromide (Spiriva Respimat) is the only LAMA registered for treatment of patients with asthma. The characteristics of the Respimat inhaler may improve tiotropium availability and minimize the negative impact of incorrect inhalation technique on treatment effectiveness. Hochrainer et al. observed that the aerosol cloud produced by the Respimat inhaler lasts much longer (ca. 1.5 s) than that produced by CFC-MDI or HFA-MDI inhalers (0.2–0.4 s). In the same study, velocity of the aerosol produced by specific inhalers was also evaluated and the most favorable result (i.e. the lowest velocity) was also that of Respimat (< 1 m/s at 10 cm from

the mouthpiece). Moreover, the share of small particles (60–70%) in the aerosol cloud generated by Respimat is also favorable. In addition, *in vitro* studies demonstrated that Respimat generated lower flow resistance than dry powder inhalers (DPI) [40].

It should be remembered that the objective of introduction of tiotropium in clinical practice is not to replace ICS that must remain the mainstay of asthma treatment. The proposed role of LAMA in light of the current GINA recommendations is presented in Table 3.

The following patients groups should especially benefit from addition of tiotropium to their treatment:
— those with the asthma/COPD overlap syndrome,
— those with frequent exacerbations,
— those with symptomatic asthma despite intensive pharmacological treatment (i.e. high-dose ICS and LABA),
— those with progressive deterioration of lung function,
— those with progressive obstruction of the airways,
— those with productive cough and neutrophils in the sputum,
— current smokers,
— those with a good effect of short-acting anticholinergics used as rescue medication.

Effects of suboptimal asthma control, including economic aspects

The care for patients with uncontrolled asthma generates enormous costs for the healthcare systems in both developed and developing coun-

tries. It has been demonstrated that treatment of asthma exacerbations significantly increases the planned and unplanned costs in comparison with controlled or partially controlled asthma [41]. The costs related to asthma treatment increase steadily; these include both direct (outpatient visits, hospitalizations, medications) and indirect costs (lost workdays, social services, etc). Study results indicate that the mean annual cost per patient increases while the level of disease control decreases [42]. Treatment of severe and uncontrolled asthma generates significant direct costs (pharmacotherapy, hospitalizations, and emergency interventions). Moreover, indirect costs, i.e. lost productivity and the necessity to pay welfares and disability pensions, should also be taken into account. Due to asthma exacerbations, many school and work days are lost; the situation is the best in Western Europe and the worst in Japan and Central and Eastern Europe [43]. In the TENOR study, the utilization of healthcare resources by patients in whom asthma remained symptomatic despite treatment was evaluated. It was confirmed that the lack of asthma control significantly increases the number of: lost work and school days, outpatient visits, and days spent at the hospital [44].

The quality of life of a patient with asthma in whom the optimal asthma control has not been achieved is worse in each domain, leading to systematic limitation of daily activities, and in certain cases to eventual disability. In addition, a patient with uncontrolled asthma is forced to use rescue medications more often, generating additional costs and increasing the risk of adverse effects.

Poland is one of the few European countries in which the rate of hospitalizations due to asthma has increased in the last years [45]. In a report by the Łazarski University (2014), titled "Allergic diseases — an analysis of financing of healthcare and social services", current data regarding direct and indirect costs of bronchial asthma in Poland have been presented [46]. The analysis demonstrated that the number of hospitalizations due to asthma increased in the years 2009–2013, from 32,062 in 2010 to 36,020 in 2013. The increase of costs of hospitalization of patients with asthma incurred by the National Health Fund (NHF), i.e. by PLN 10 million in 3 years (2010–2013), was also significant. The cost of a single hospitalization due to asthma in 2013 was PLN 2397, with a median of 6 days spent in the hospital (data for the year 2012). Data concerning services provided by the Social Insurance Institution have also been published. In 2013, 67,700 medical certificates of temporal incapacity for work due to bronchial asthma were issued. The mean number of workdays lost due to the disease was 21.98 per patient with asthma. Incapacity for work benefits are also paid to patients with asthma — in 2012, 16,000 Polish citizens received such benefits to the amount of PLN 157 million. In 2013, 240 new benefit decisions were related to asthma. In 2012, total costs related to incapacity for work benefits due to asthma, incurred by the Social Insurance Fund, the state budget, and employers, amounted to PLN 209 million.

Summary and recommendations of the expert group

Uncontrolled asthma is a serious health and social problem, leading eventually do respiratory disability, and generating high costs for the healthcare system.

In Poland, costs related to lost productivity and reduced daily activities of the patient are still not taken into account. In reimbursement decisions, indirect costs increasing the total costs of adequate care are also ignored. Reimbursement of new medications with rational treatment costs would increase the range of available treatment options and improve the chance of achievement of desired effects of treatment in patients with severe and uncontrolled asthma.

Conflict of interest

Anna Bodzenta Łukaszyk, Andrzej M. Fal, Ewa Jassem, Marek Kowalski, and Piotr Kuna were members of the Advisory Board of "Tiotropium Respimat in Asthma" (Warszawa, 11/13/2014) organized by Boehringer Ingelheim.

References

1. Braido F. Failure in asthma control: reasons and consequences. Scientifica (Cairo) 2013; 2013: 549252–15.
2. Global strategy for asthma management and prevention. Available on: http://www.ginasthma.org/local/uploads/files/GINA_Report_2015.pdf; 7.05.2015.
3. Chung KF, Wenzel SE, Brozek JL et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343–373. doi: 10.1183/09031936.00202013.
4. Łukaszyk M, Łukaszyk E, Budny W, Skiepko R, Ziętkowski Z, Bodzenta-Łukaszyk A. Astma ciężka — wytyczne międzynarodowe w roku 2014. Alergologia Info 2014; 4: 131–133.
5. Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998; 12: 1209–1218.
6. Kowalski ML, Jędrzejczak M, Cirlić M. Efektywność leczenia astmy oskrzelowej w polsce w ocenie pacjentów — wyniki badania AIRCEE (Astma Insights&Reality in Central and Eastern Europe). Alergia Astma Immunologia 2004; 9: 187–195.
7. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking

in relation to asthma control. Prim Care Respir J 2009; 18: 300–305.

8. Weinstein AG. The potential of asthma adherence management to enhance asthma guidelines. Ann Allergy Asthma Immunol 2011; 106: 283–291. doi: 10.1016/j.anai.2011.01.016.

9. Bateman ED, Boushey HA, Bousquet J et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004; 170: 836–844.

10. Langmack EL, Martin RJ. Heterogeneity of response to asthma controller therapy: clinical implications. Curr Opin Pulm Med 2010; 16: 13–18. doi: 10.1097/MCP.0b013e328333af9c.

11. Jacquemin B, Kauffmann F, Pin I et al. Air pollution and asthma control in the Epidemiological study on the Genetics and Environment of Asthma. J Epidemiol Community Health 2012; 66: 796–802.

12. Siroux V, Boudier A, Bousquet J et al. Phenotypic determinants of uncontrolled asthma. J Allergy Clin Immunol 2009; 124: 681–7.e3. doi: 10.1016/j.jaci.2009.06.010.

13. Boulet L-P, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. Clin Chest Med 2012; 33: 405–417. doi: 10.1016/j.ccm.2012.06.002.

14. Spector S. Noncompliance with asthma therapy — are there solutions? J Asthma 2000; 37: 381–388.

15. Gamble J, Stevenson M, McClean E, Heaney LG. The Prevalence of Nonadherence in Difficult Asthma. Am J Respir Crit Care Med 2012; 180: 817–822. doi: 10.1164/rccm.200902-0166OC.

16. Murphy AC, Proeschel A, Linnett ME et al. P174 Identifying non-adherence with asthma medication and the relationship to clinical outcomes amongst adults with difficult-to-control asthma. Thorax 2010; 65 (Suppl 4): A151–A151.

17. Foster JM, Smith L, Bosnic-Anticevich SZ et al. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. Intern Med J 2012; 42: e136–44. doi: 10.1111/j.1445-5994.2011.02541.x.

18. Wilson SR, Strub P, Buist AS, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med 2010; 181: 566–577. doi: 10.1164/rccm.200906-0907OC.

19. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. BMC Pulm Med 2010; 10: 1. doi: 10.1186/1471-2466-10-1.

20. Brinke ten A, Sterk PJ, Masclee AAM et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005; 26: 812–818.

21. Robinson DS, Campbell DA, Durham SR et al. Systematic assessment of difficult-to-treat asthma. Eur Respir J 2003; 22: 478–483.

22. Aaron SD, Vandemheen KL, Boulet L-P, et al. Overdiagnosis of asthma in obese and nonobese adults. CMAJ 2008; 179: 1121–1131. doi: 10.1503/cmaj.081332.

23. Melani AS, Bonavia M, Cilenti V et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011; 105: 930–938.. doi: 10.1016/j.rmed.2011.01.005.

24. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. Eur Respir J 2002; 19: 246–251

25. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. Respir Care 2005; 50: 1360–1374.

26. Dolovich MA, MacIntyre NR, Anderson PJ et al. Consensus statement: aerosols and delivery devices. American Association for Respiratory Care 2000; 45: 589–596.

27. Norman G, Faria R, Paton F et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Health Technol Assess 2013; 17: 1–342. doi: 10.3310/hta17520.

28. Beasley RW, Donohue JF, Mehta R et al. Effect of once-daily indacaterol maleate/mometasone furoate on exacerbation risk

in adolescent and adult asthma: a double-blind randomised controlled trial. BMJ open 2015; 5: e006131. doi: 10.1136/bmjopen-2014-006131.

29. Kempsford R, Norris V, Siederer S. Vilanterol trifenatate, a novel inhaled long-acting beta2 adrenoceptor agonist, is well tolerated in healthy subjects and demonstrates prolonged bronchodilation in subjects with asthma and COPD. Pulm Pharmacol Ther 2013; 26: 256–264. doi: 10.1016/j.pupt.2012.12.001.

30. Bateman ED, O'Byrne PM, Busse WW et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax 2014; 69: 312–319. doi: 10.1136/thoraxjnl-2013-203600.

31. Woodcock A, Bleecker ER, Lötvall J et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest 2013; 144: 1222–1229. doi: 10.1378/chest.13-0178.

32. Kato M, Komamura K, Kitakaze M. Tiotropium, a novel muscarinic M3 receptor antagonist, improved symptoms of chronic obstructive pulmonary disease complicated by chronic heart failure. Circ J 2006; 70: 1658–1660.

33. Timmer W, Moroni-Zentgraf P, Cornelissen P, Unseld A, Pizzichini E, Buhl R. Once-daily tiotropium Respimat(®) 5 μg is an efficacious 24-h bronchodilator in adults with symptomatic asthma. Respir Med 2015; 109: 329–338. doi: 10.1016/j.rmed.2014.12.005.

34. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 2003; 124: 1743–1748.

35. Casaburi R, Mahler DA, Jones PW et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002; 19: 217–224.

36. Peters SP, Kunselman SJ, Icitovic N et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010; 363: 1715–1726. doi: 10.1056/NEJMoa1008770.

37. Kerstjens HAM, Engel M, Dahl R et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012; 367: 1198–1207.

38. Fitzgerald JM, Kerstjens H, Paggiaro P et al. Once-daily tiotropium Respimat® add-on to ICS±LABA improves control across asthma severities. Eur Respir J 2014; 44 (Suppl 58): 1894.

39. Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. Respir Med 2008; 102: 50–56.

40. Ciciliani A, Langguth P, Bickmann D, Wachtel H, Voshaar T. Poster presented at the ISAM 2013 Conference, Chapel Hill, NC, USA, April 06-10, 2013.

41. Vervloet D, Williams AE, Lloyd A, Clark T. Costs of managing asthma as defined by a derived Asthma Control TestTM score in seven European countries. Eur Respir Rev 2006; 15: 17–23.

42. Bahadori K, Doyle-Waters MM, Marra C et al. Economic burden of asthma: a systematic review. BMC Pulm Med 2009; 9: 24. doi: 10.1186/1471-2466-9-24.

43. Rabe KF, Adachi M, Lai CKW et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol 2004; 114: 40–47.

44. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE, TENOR Study Group. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. Allergy 2007; 62: 126–133.

45. Age-standardised admission rates for asthma for earliest and latest available year in European countries ordered by latest admission rate. Available on: http://www.globalasthmareport.org/charts/Ch3_Fig1.html; 7.05.2015.

46. Gałązka-Sobotka M. (ed.) Choroby alergiczne — analiza finansowania świadczeń zdrowotnych i społecznych. Instytut Zarządzania w Ochronie Zdrowia Uczelni Łazarskiego, Uczelnia Łazarskiego, Warszawa 2014.