Bronchial asthma ranks among the most common allergic diseases in children. It is chronic inflammatory disease of the respiratory tract, in which many cells of innate and adaptive immune system participate together with epithelial cells causing the main clinical syndromes typical for the disease. Currently, bronchial asthma therapy aims at obtaining the control over the symptoms and course of asthma by providing an anti-inflammatory baseline therapy using different groups of pharmaceuticals: inhaled glucocorticosteroids, leukotriene receptor antagonists, cromones, beta-2-agonists and long-acting theophyllines, systemic glucocorticosteroids and anti-IgE-therapy. However, despite a wide range of approaches to anti-inflammatory baseline therapy, it is still a problem to obtain the disease control in most patients indicating the necessity for searching new therapeutic approaches. In this regard, to optimize pathogenetic therapy of bronchial asthma, the work is being currently carried out to improve the existing anti-inflammatory drugs and their combinations. Moreover, there is a search for crucially new approaches to asthma treatment with due consideration of the disease phenotypes and endotypes including development and practical application of pharmaceutical drugs with anti-cytokine and anti-mediator effects. Probably, as far as the knowledge of molecular characteristics of asthma endotypes is being refined, and there being introduced the biomarkers enabling to diagnose asthma phenotypes and endotypes and monitor asthma control, there will be implemented an individual approach in individual therapy administration.

Key words: bronchial asthma; children; bronchial asthma control; baseline anti-inflammatory therapy of bronchial asthma.
in a patient, the release of inflammatory neurokinins (substance P, neurokins A and B) by nerve cells, and associated viral, bacterial or atypical (chlamydial, mycoplasmal) infections [18–22].

Since asthma is characterized by recurrent variable respiratory obstruction, the disease control can be assessed relying on the intensity of its symptoms, external respiration parameters, the findings of functional tests showing bronchial patency variability, and bronchial hyper-reactivity [23, 24]. Due to the fact that respiratory inflammation plays a key role in asthma pathogenesis, inflammation monitoring is to be the main component of patients’ management. Currently, the most extensively studied inflammation biomarker in BA is the level of nitric oxide and its metabolites in exhaled air [25–28]. Therefore, cellular composition of induced sputum, the components of expiratory air condensate (pH, leukotrienes, aldehydes and other parameters) are being under study [29–35]. A new analytical method to detect biomarkers in expiratory air condensate is metabolomics [36]. Biomarkers can be also used to diagnose basic phenotypes and endotypes of asthma. For example, the levels of Feno, serum periostin, eosinophilic neurotoxin and osteopontin can be used to diagnose and monitor Th2-dependent eosinophilic inflammation in BA [37, 38].

Allergic inflammation persistence in the respiratory tract underlies the uncontrolled BA course. To obtain complete control over asthma is the primary objective of asthma treatment [23]. Considering that respiratory inflammation is the main pathogenic component determining BA course there is the necessity for anti-inflammatory treatment as baseline therapy [39]. To obtain and maintain the control over BA symptoms and course the following pharmaceuticals are used: inhaled glucocorticosteroids (GCS), leukotriene receptor antagonists, cromones, beta-2-agonists and long-acting theophyllines [40, 41]. In severe asthma and resistant to the mentioned pharmaceuticals, systemic GCS and anti-IgE-therapy are used [42]. Moreover, for pathogenetic BA therapy other drugs are being developed now — pharmaceutical drugs with anti-cytokine and anti-mediator effects [43].

**Glucocorticosteroids**

Glucocorticosteroids exhibit high anti-inflammatory and anti-allergic action related to its capacity to activate anti-inflammatory genes and suppress many pro-inflammatory genes initiated in the course of inflammation (Table 1). As a result, there is the inhibition of synthesis of pro-inflammatory cytokines and lipid mediators (leukotriene, prostaglandins), retardation of eosinophil participation in the development of allergic inflammation and excretion of eosinophilic mediators [44–46].

Primarily, in BA inhaled GCS are administered to neutralize systemic side effects common to GCS. As a result of treatment, on day 5–7 of therapy most patients

| Table 1 | The effect of glucocorticosteroids on transcription related to asthma genes [45] |
| Transcription increase (transactivation) | Transcription decrease (transrepression) |
| Lipocortin-1 | Pro-inflammatory cytokines: IL-2, IL-3, IL-4, IL-5, IL-6, IL-13, IL-15, TNF-α, GM-CSF, SCF, TSLL |
| β2-adrenoreceptors | Chemokines: CCL1, CCL5, CCL11, CXCL8 |
| Secretory leukocyte inhibitory protein | Proinflammatory enzymes: iNOS |
| Lxβ-α — inhibitor of NF-κB | (inducible nitric oxide synthase); |
| Anti-inflammatory cytokines | inducible phospholipase A2 — cPLA2 |

| Table 2 | Equipotent daily doses of inhaled glucocorticosteroids for children with bronchial asthma |
| Inhaled GCS | Daily dose (µg) |
| | Low | Median | High |
| Beclometasone dipropionate | 100–250 | 250–500 | >500 |
| Budesonide | 100–200 | 200–600 | >600 |
| Fluticasone propionate | 100–200 | 200–400 | >400 |
| Ciclesonide | 100 | ≥200 | >400 |
| Mometasone furoate | 80–160 | 160–320 | ≥320 |

with incomplete BA control were found to have broncho-obstructive syndrome disappeared. By the third week of treatment there was respiratory function normalization, and nonspecific bronchial hyper-reactivity decrease. The therapy of starter doses of inhaled GCS generally lasts for 3 months, and in case there are no symptoms, the daily dose is reduced to a maintaining dose to prevent asthma recurrence. Patients can receive a maintaining dose for a few years. The application of inhaled GCS improves the quality of life in BA patients.

Currently, the following inhaled GCS are used to provide anti-inflammatory baseline therapy in BA children: beclometasone dipropionate, budesonide, ciclesonide, fluticasone propionate, mometasone furoate. These medications have high affinity for GCS receptors, and are able to reach high and long keeping therapeutic concentrations in tissues when locally administered. They rapidly inactivate due to biotransformation in the liver after systemic absorption. High local anti-inflammatory activity and low systemic bioavailability are the main factors of efficacy and safety of inhaled GCS [45]. Table 2 shows equipotent daily doses of these drugs for children with BA.

**Beclometasone dipropionate** is inhaled GCS with high anti-inflammatory activity and an insignificant systemic effect. It has been used in BA therapy for 40 years and shown its clinical efficiency and safe profile in children and adults with chronic persistent asthma [47, 48]. Beclometasone dipropionate is a prodrug,
which hydrolyzes in the lungs to beclometasone monopropionate. And beclometasone monopropionate, in its turn, hydrolyzes to beclometasone. A daily dose of beclometasone monopropionate is 200–1200 μg and administered 3–4 intakes.

Beclometasone monopropionate is an active substance in aerosol spray Clenil Get. A jet-system increases aerosol deposition in the lungs and reduces deposition of its particles in oropharynx that enables to reduce the risk of oropharyngeal candidosis, cough, hoarseness, and systemic effect of the drug. One inhalation dose contains 200 or 250 μg beclometasone monopropionate.

6–12-year-old-children are administered 250 μg b.i.d., a daily dose for children over 12 years with mild form of the disease is 200–600 μg for 2 inhalations, in moderate asthma — 600–1000 μg for 2–4 inhalations, in severe asthma — 1000–2000 μg for 2–4 inhalations [49].

Clenic UDV based on beclometasone monopropionate for nebulizer BA therapy is produced in the form of suspension in ampoules containing 800 μg of beclometasone monopropionate. Children over 6 years are administered the medication by a half of an ampoule for nebulation at the dose of 400 μg 1–2 times a day [48].

Budesonide is the only non-halogenated inhaled GCS, has been used in asthma therapy for 35 years. 90% of budesonide metabolizes in the liver and excrettes from the body in the form of inactive metabolites. When interacting with fatty acids in cells, budesonide forms complexes, which are intracellular drug reservoir [50].

Pulmicort Turbuhaler is budesonide powder delivered in bronchi by turbuhaler. One inhalation dose of Pulmicort Turbuhaler contains about 200 μg of the agent. Pulmicort Turbuhaler is administered to children over 7 years at the dose of 400–800 μg for 2–4 intakes.

Pulmicort-based suspension manufactured in nebulas (for nebulizer therapy) has become widely used to treat BA exacerbations in children. There has also been used an analogue of Pulmicort — Budenil Steri-Neb, dosing suspension. To treat BA in children Pulmicort suspension dose is selected individually: an initial dose for 6-month-children and older is 0.25–0.5 mg/day. If necessary, a dose can be increased to 1 mg/day.

Benacort is a budesonide-based domestic GCS drug. It is powder in a cyclohaler containing 400 budesonide doses. Sodium benzoate is used as a filler, as it has antifungal activity [51]. Another form of Benacort is inhalation powder in the form of capsules (200 doses) used for children over 7 years, a daily dose being 400–800 μg for 2–3 intakes [52].

Fluticasone propionate exhibits marked anti-inflammatory activity [53]. The administration of this inhaled GCS for 6 months and more enables to obtain BA control and reach clinical remission.

Fluxotide is dosing aerosol manufactured in bottles containing 60 (120) inhalation doses of 125/250 μg of the agent. It comes pre-loaded with blisters containing individual doses of the medicine as a powder. One dose may contain 50, 100, 250 and 500 μg of fluticasone propionate. Depending on BA severity, Fluxotide is administered in children over 4 years, a daily dose being 100–500 μg for 2 intakes.

Ciclesonide is an extra-finely divided inhaled GCS. Ciclesonide deposits both in central and peripheral bronchial parts. It is a prodrug by its mechanism of action, as it activates in endothelial cells of the respiratory tract forming an active metabolite — des-ciclesonide with hundredfold affinity to GCS receptors compared to ciclesonide. Ciclesonide therapy promotes BA control, it having high clinical efficiency.

Alvesco is manufactured in aerosol packs containing 40, 80 and 160 μg in one inhalation dose. It is used in BA in 6-year-old children and over. A dose is 80–300 μg depending on BA severity [54, 55].

Mometasone furoate is GCS with the highest affinity for GCS receptors compared to other inhaled GCS used in BA. Its long half lifetime correlates with high therapeutic efficiency and safety.

The advantage of Asmanex Twisthaler is the possibility to use it once a day that contributes to patients’ compliance increase. Pharmaceutical form (200 and 400 μg) complies with the requirements for sequential BA therapy, and enables to increase or reduce a dose due to the characteristics of asthma control [56].

Therapy of low and median doses of inhaled GCS minimizes systemic side effects. However, when administering inhaled GCS therapy one should take into consideration a child’s height and recommend to use minimum effective doses in all children with BA [57]. Inhaled GCS are the most effective anti-inflammatory drugs providing control over the symptoms and courses of most BA cases. However, there are cases of steroid-resistance requiring dose increase that is presents an increase in risk of unfavorable side effects.

Understanding of molecular mechanisms of GCS action enables to consider in detail the causes of GCS resistance formation [58]. Currently, there has been found that innate steroid-resistance related to mutation in the gene encoding GCS receptors is very rare in BA [59, 60]. More frequently, there is acquired steroid-resistance, which is, primarily, due to GCS receptor modification in asthma: when exposed to Th2-proinflammatory cytokines, the products of nitrosylating and oxidative stress, microbial and fungal super-antigens, and their degradation in response to proteases [61]. The problem of steroid-resistance now is being attempted to solve in two ways. On the one hand, BA phenotypes and endotypes are being studied intensively in order to determine the cohorts of patients, whose pathogenetic characteristics of the disease are responsible for initial resistance to GCS (e.g., Th17-mediated, primarily, neutrophil variants of inflammation in BA) [62]. On the other hand, there have been intensively developed new approaches to increase anti-inflammatory GCS activity, decrease the probability of unfavorable side effects.
of these drugs. The work is being carried out in three directions.

1. Combination therapy: the second medicinal product is added to inhaled GCS to overcome steroid-resistance and reduce GCS doses necessary to reach the clinical effect. Long-acting beta-2-agonists exhibit such properties. Currently, novel pharmaceuticals are under clinical trials, such as selective inhibitors p38-MAPK (mitogen-activated protein kinase) [63]. Inhibitor p38-MAPK has an effect on transcription of genes encoding synthesis of many pro-inflammatory cytokines including TNF-α, IL-4, IL-5, IL-8, RANTES and eotaxin, and so asthma pathogenesis as well. Some manifestations of steroid-resistance can be neutralized by small doses of theophylline [64]. Application of antioxidants is considered as emerging [61].

2. Development of prodrugs (by ciclesonide type, which turns into its active form in the lungs — C21-de-methylpropionyl-ciclesonide accompanied by low oral-pharyngeal absorption), as well as medications with high affinity to GCS receptors that enables to administer the drugs once a day (ciclesonide, fluticasone furoate, mometasone furoate) [65].

3. Development of dissociated GCS, which would have effects different in their intensity on gene transrepression and transactivation that would enable to modulate unfavorable side effects of these drugs as well [45].

**Fixed dose combination of GCS and long-acting beta-2-agonists**

Combination therapy is one of the approaches to improve the efficiency of inhaled GCS and surmount their steroid-resistance in BA. The most applicable in practice are fixed combinations of GCS and long-acting beta-2-agonists: fluticasone propionate and salmeterol xinafoat (Seretide, Tevacombo), budesonide and formoterol fumarate (Symbicort), beclometasone dipropionate and formoterol fumarate (Foster). Combined therapy by combination drugs is the most effective treatment of children with severe and moderate severe BA compared to isolated application of inhaled GCS.

**Fluticasone propionate + salmeterol xinafoate** (original combination: Seretide, GlaxoSmithKline, Great Britain) is manufactured as dry powder inhalator — Seretide Multidisk, one dose containing 50 μg of salmeterol xinafoat and 100, 250 and 500 μg of fluticasone propionate, and as dose aerosol inhaler (without freon), each dose containing 25 μg of salmeterol xinafoat and 50, 125 and 250 μg of fluticasone propionate. It is used for children since the age of four. Seretide dose is determined due to child’s age and BA severity. Therapy success appears as reduced number of BA symptoms and exacerbations, and the achievement of clinical remission in some patients. It has high tolerability.

**Formoterol fumarate + budesonide** (original combination: Symbicort Turbuhaler, Astra Zeneca, Sweden) is used for inhalations in children since the age of 6. 6–12-year-old children are administered the medicinal product according to the following schedule: 100/5 μg a day is comparable to that of 250/50 μg of fluticasone propionate + salmeterol twice a day in patients with persistent asthma uncontrolled by medium doses of inhaled GCS after 24-week therapy [71].

**Mometasone furoate + formoterol fumarate** is an original combination of Zenhale, 3M Health Care Ltd. (USA); Organon (Ireland). The recommended dosages of 100/5 and 200/5 μg twice a day to treat BA in adolescents and adults [72].

**Fluticasone propionate + formoterol fumarate** is an original combination, Flutiform, SkyPharma (Switzerland). The dose of 250/10 μg has been shown to provide higher efficiency than monotherapy (fluticasone propionate) to control moderate severe and severe BA, with safety profile similar to fluticasone propionate monotherapy [69, 70].

The administration of inhaled GCS and fixed-dose combination is reasonable, primarily, in persistent moderate severe or severe BA. They are ineffective in mild persistent asthma, though not so much needed, since the control can be obtained by non-steroid anti-inflammatory therapy as well (cromones, leukotriene receptor antagonists).

The alternative of long-acting beta-2-agonists in some cases is supposed to be long-acting anticholinergics including those combined with inhaled GCS. Currently, the idea provokes
### Table 3

Some of new pharmaceuticals for bronchial asthma therapy ([43] revised)

<table>
<thead>
<tr>
<th>Therapeutic category, medication name</th>
<th>Manufacturer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticosteroid + long acting (\beta)-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone furoate / formoterol fumarate</td>
<td>SkyPharma, Switzerland</td>
<td>[69, 70]</td>
</tr>
<tr>
<td>Fluticasone furoate + vilanterol trifenate</td>
<td>Theravance Inc. (USA); GlaxoSmithKline (Great Britain)</td>
<td>[71]</td>
</tr>
<tr>
<td>Mometasone furoate + indacaterol maleate</td>
<td>Novartis Pharma AG (Great Britain)</td>
<td>[72]</td>
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<tr>
<td><strong>Inhaled long-acting anticholinergics</strong></td>
<td></td>
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<tr>
<td>Tiotropium bromide</td>
<td>Boehringer Ingelheim (Germany); Pfizer (USA)</td>
<td>[73]</td>
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<tr>
<td>Acicteinium bromide</td>
<td>Forest Laboratories Netherlands B. (Netherlands); Almirall Hermal GmbH (Germany); Almirall Prodesfarma (Spain)</td>
<td>[74]</td>
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<tr>
<td>Umeclidinium bromide</td>
<td>Theravance Inc. (USA); GlaxoSmithKline (Great Britain)</td>
<td>[75, 76]</td>
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<tr>
<td><strong>Inhaled long-acting anticholinergics + corticosteroids</strong></td>
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<tr>
<td>Umeclidinium bromide + fluticasone furoate</td>
<td>GlaxoSmithKline (Great Britain)</td>
<td>[75, 76]</td>
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<tr>
<td><strong>Anti-cytokine and anti-mediator therapy</strong></td>
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<tr>
<td><strong>Target — IL-5:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Reslizumab</td>
<td>Teva (Israel)</td>
<td>[77]</td>
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<tr>
<td>Benralizumab</td>
<td>MedImmune, LLC (USA)</td>
<td>[78]</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>GlaxoSmithKline (Great Britain)</td>
<td>[79]</td>
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<tr>
<td><strong>Target — IL-13:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>MedImmune, LLC (USA)</td>
<td>[80, 81]</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>Genentech Inc. (USA)</td>
<td>[81]</td>
</tr>
<tr>
<td><strong>Target — IL-4/IL-13:</strong></td>
<td></td>
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<tr>
<td>Dupilumab</td>
<td>Sanofi (France); Regeneron (USA)</td>
<td>[82]</td>
</tr>
<tr>
<td><strong>Receptor antagonists</strong></td>
<td></td>
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<tr>
<td>OC000459</td>
<td>Oxagen Ltd. (Great Britain)</td>
<td>[83, 84]</td>
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considerable interest [85–87]. Accordingly, long-acting anticholinergics are being actively studied.

**Tiotropium bromide**, including that combined with inhaled GCS, is under phase III of clinical trials to study its possible application in asthma therapy in children and adolescents. When administered in adult subjects, it resulted in significant decrease of exacerbation rate [73].

**Umeclidinium bromide** is currently being under clinical trials, phase II, for possible use in asthma treatment as both monotherapy and a part of combination therapy with inhaled GCS [75, 76].

**Acicteinium bromide.** The researches carried out have demonstrated its bronchodilating and anti-inflammatory effect [74].

Non-steroidal anti-inflammatory drugs

Leukotriene receptor antagonists have widespread application in bronchial asthma therapy in children.

**Montelukast sodium** (Singulair, Montelar, Montelast, Singlon) inhibits cysteinyl leukotriene receptors used in children since 2 years. Its dose for 2–5-year-old children is 4 mg in a chewable tablet, at the age of 6–14 years — 5 mg in a chewable tablet, once a day, for children of 15 years and over — one coated tablet, 10 mg daily. The medication prevents day and night BA symptoms, reduces exacerbations in aspirin-sensitive, virus-induced asthma and exercise induced asthma, minimizes manifestations of associated allergic rhinitis, persistent and intermittent rhinitis [88, 89]. Montelukast sodium is used as monotherapy to control mild asthma; in combination with inhaled GCS can be effective in moderate severe or severe BA enabling to reduce GCS dose. This medication is used also in case of GCS withdrawal or dose reduced to maintain BA control attained. Montelukast sodium exhibits high tolerability, headache and nausea occurring rarely [90].

**Theophylline** has been used to treat respiratory diseases for over 100 years. It was initially administered
as bronchodilator. However, relatively high doses necessary for bronchial obstruction arrest cause unfavorable side effects; therefore its application for that purpose has been reduced. However, theophylline in lower concentrations is characterized by anti-inflammatory effects due to PDE4 inhibition and histone deacetylase-2 activation, with the result that activated inflammatory genes are knocked out. Through this mechanism theophylline reduces steroid-resistance that can be of particular concern in patients with severe asthma. Methylxanthine medications inhibit A1-receptors to adenosine causing a bronchodilating effect, suppress the release of inflammatory mediators by mast cells and basophils, and enhance apoptosis of eosinophils inhibiting respiratory inflammation. Currently, in BA therapy there used primarily low doses of slowly released theophyllines (Neotohe-Pecum A, Theopec, Ventax, Teotard, Eliphyllyne, etc.). In children with BA prolonged theophyllines can be administered for the anti-inflammatory purpose at low doses as a component of baseline therapy for 1–2 months. Repository theophylline therapy contributes to reduced number of asthmatic attacks, the increase of effort tolerance, and in some patients inhaled GCS dose reduction. Theophylline tolerance in such doses in most children is high. In individual cases there can be sleep disturbance, tachycardia, nausea, vomiting, headaches due to phosphodiesterase inhibition, higher doses can cause cardiac arrhythmia [64].

Additional administration of Montelukast sodium and repository theophylline enables to improve therapy efficacy and obtain asthma control in children with severe BA with inadequate efficacy of inhaled GCS and long-acting beta-2-agonists.

**Roflumilast**, phosphodiesterase 4 inhibitor, has approved indication for patients with chronic obstructive pulmonary disease. Its potential anti-inflammatory effects have been shown in a randomized placebo-controlled clinical study in patients with mild allergic asthma [91].

Cromones (cromoglicic acid and sodium nedocromil) are able in exposition with causally significant allergen to prevent bronchospasm development, an early and late phase of allergic reaction, inhibit the increase of bronchoreactivity. They are effective primarily in children with mild BA [92]. These medications have an insignificant effect on disease exacerbation once developed [93].

**Cromoglicate sodium** is manufactured both as dose aerosol, and 2% solution of nebulized 2 ml-inhalations. Inhalation frequency of cromoglicic acid is 4 times a day. Baseline therapy requires long administration, at least 3 months. In mild asthma, cromoglicate sodium is used to prevent seasonal exacerbations of the disease and BA exacerbations on physical exertion. The medication has high tolerability. Side effects are rare, and occur mainly as local reaction in the form of reactive airway disease, cough, and rarely — a bronchospasm [94].

**Nedocromil sodium (Tilade)** suppresses the release of inflammation mediators from mast cells, eosinophils, neutrophils, monocytes, macrophages and platelets, inhibits bronchospasm development, late allergic reactions, and reduces nonspecific hyper-reactivity of bronchi and BA exacerbation rate. The medication is manufactured as dosed aerosol, 2 ml, for children over 2 years (1 inhalation dose) 2–4 times a day [93].

### Biological treatment modalities in bronchial asthma

**Anti-IG-E-therapy.** In severe, refractory to conventional pharmacotherapy BA course, anti-IG-E-therapy based on parenteral administration of anti-IG-E-antibodies in the form of omalizumab (Xolair) can be effective. Omalizumab binds free-circulating IgE in blood, reduces the production of high-affinity receptors on membrane of mast cells and basophils resulting in decreased excretion of mediators, allergic inflammation intensity and BA exacerbation regression [95–97]. Before treatment initiation, an individual dose of omalizumab is calculated considering total IgE level in peripheral blood and child’s body mass, the medication being administered subcutaneously. Omalizumab promotes the reduction of BA exacerbation rate, the number of admissions to hospital and visits to a doctor, decrease of baseline therapy when obtaining complete control over the disease in most cases. In some cases after the medication administration patients may suffer from headache, and in the site of its subcutaneous injection there may occur edema, erythema and itching. The main indication for omalizumab administration is severe BA in children aged 6 and over, refractory BA to pharmacotherapy [98].

**Anti-cytokine therapy.** Based on common knowledge on Th2-dependent asthma genesis and eosinophilic respiratory inflammation in this disease, anti-cytokine therapy, in addition to IgE, also targets interleukins IL-5, IL-13, IL-4, IL-9 [99].

**Anti-interleukin-5-antibodies.** IL-5 is involved in the activation and maturation of eosinophils. Anti-IL-5-antibodies — Mepolizumab is being under clinical study, phase III, DREAM, which involved patients aged 12–74 years with recurrent severe BA and the signs of eosinophilic inflammation. It showed the therapy efficacy including BA exacerbation reduction by 52% annually [79, 100]. Currently, within the frame of III phase of clinical trials there being studied the antibodies to IL-5 receptor (Benralizumab); within a few months after a single injection of the medication there are the effects of eosinophil exhaustion [78].

**Anti-interleukin-13-antibodies.** IL-13, an essential BA mediator, produces the most of BA characteristics in experimental models including mucus remodeling, hyperproduction, IgE synthesis, recruitment of eosinophils and basophils [101]. For effective assessment of anti-IL-13-therapy, peristin, a novel...
serum asthma biomarker is used, which is a component of extracellular matrix isolated from epithelial respiratory cells in response to IL-13 and IL-4. Its release is inhibited by GCS [102, 103]. Serum periostin content enables to differentiate patients with “expressed” and “unexpressed” Th2-phenotype of BA [12, 104]. Specific anti-IL-13-antibodies are the following drugs: Lebrikizumab, Tralokinumab, Anrurikumab [80, 81]. Lebrikizumab is injected subcutaneously once a month. A randomized multi-center study (219 patients) has shown it to be more effective in patients with higher initial periostin level in blood serum [100, 80, 105].

Anti-interleukin-4-antibodies. IL-4 is involved in differentiation of Th2-cells switching to IgE synthesis, recruitment of eosinophils and mast cells. Altrakincept is soluble recombinant human receptor to IL-4 meant for inhalation therapy. The medication neutralizes the activation of immune and other cells caused by IL-4. A single inhalation in adults with moderate asthma results in pulmonary function improvement and reduced level of expired nitric oxide [106]. Pitrakintra — an antagonist of heterodimeric receptor complex (IL-4R-IL-13Pa) — has been developed to overcome biological redundancy of IL-4 and IL-13 that is likely to compensate inefficiency of strategies targeting IL-4 [107]. Pitrakinra inhibits allergen-induced allergic reactions and disease exacerbations in adults with eosinophilic asthma [108].

AMG 317 is a monoclonal antibody targeting receptors to IL-4; it blocks IL-4 binding with its receptor, as well as inhibits IL-13 signal transduction. In adult patients with moderate and severe asthma, AMG 317 produces significant clinical improvement only in a group of patients without disease control [109]. Dupilumab is one of the last medications of anti-IL-4-therapy; it has an effect on alpha-subunit of IL-4 receptor. Its administration in patients with eosinophilic asthma due to inhibition of both IL-4 and IL-13 is accompanied by significant reduction of BA exacerbations and improved pulmonary function in adults with persistent asthma, withdrawal of beta-agonists and reduced dose of inhaled GCS [82].

OCO004559 is an oral CRTH2 (chemo-attractant receptor of Th2-helper homologous molecule) antagonist. In a randomized double blind clinical trial (phase II) in adults with moderate persistent asthma, the use of oral antagonist of CRTH2 was accompanied by improved pulmonary function, the alleviation of night symptoms and the improvement of life quality compared to placebo [83, 84].

MEDI-528 is anti-IL-9-antibodies. The use of this medication has shown the tendency for improvement of control indices in adult patients with mild and moderate asthma, as well as a protective effect against bronchospasm [110].

Potential targets of new approaches to BA therapy under development are TSLP, IL-25 and IL-33 molecules produced by epithelial respiratory cells in response to allergens or viral triggers, therefore they can be considered as possible targets when developing novel asthma treatment modalities [103, 111].

Targeted neutrophilic inflammation therapy. Neutrophilic inflammation in BA is associated with interleukins IL-17 and IL-23. Secukinumab — anti-IL-17-antibodies — are being currently under clinical trial, phase II [112].

It should be noted that national and international conciliation documents recommend a staged approach to achieve and maintain BA control. Transition to the next or previous stage can be made within a given period depending on BA severity, against the assessment of the disease control under routine medical supervision. Control achievement in atopic asthma is promoted by allergen-specific immune therapy by causally significant allergens and their level reduction in the patient’s environment [15, 99, 113–115]. BA monitoring in children includes pulmonary function test, exhaled nitric oxide concentration test, and bronchoreactivity assessment [27, 116]. Obtaining and maintenance of asthma control are promoted by educational programs for parents and asthmatic children. In case of BA attacks, there being applied the inhalation therapy of short-acting beta-2-agonists or fixed dose combinations (Berodual) using dosed inhalers and nebulizers. In severe asthmatic attacks, inhaled and systemic GCS (per os or parenterally) therapy is administered. In status asthmaticus, infusion therapy by Euphyline and GCS appears to be effective.

Conclusion. Despite a wide range of medications for anti-inflammatory baseline therapy and emergency drugs, it is still a problem of uncontrolled and poorly controlled bronchial asthma course, so it determines the necessity for developing additional diagnostic and therapeutic approaches. In this regard, to optimize pathogenetic therapy of bronchial asthma, the work is being currently carried out to improve the existing anti-inflammatory drugs and their combinations. Moreover, there is a search for crucially new approaches to asthma treatment with due consideration of the disease phenotypes and endotypes including development and practical application of pharmaceutical drugs with anti-cytokine and anti-mediator effects. It is hoped that as far as the knowledge of molecular characteristics of asthma endotypes is being refined, and there being introduced the biomarkers enabling to diagnose asthma phenotypes and endotypes and monitor asthma control, there will be implemented an individual approach in individual therapy administration.

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