Mepolizumab: a new drug programme for patients with severe eosinophilic asthma

DOI: 10.7365/JHPOR.2018.1.4

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Keywords:

omalizumab, reslizumab, severe asthma, drug programme, benralizumab, mepolizumab

Abstract

Biological treatment involves more and more fields of medicine. This also applies to severe asthma for which a therapy with omalizumab (anti-IgE antibodies for patients with allergic asthma) has been available since 2013, completed by mepolizumab since 1st November 2017 - available in a new drug programme. Mepolizumab is a humanised monoclonal antibody (IgG1, κ), against human interleukin-5 (IL-5), which significantly impacts proliferation, maturation in bone marrow and recruitment and activation of eosiniphils at inflammatory site. It is also considered to be the only eosinophilopoietic factor. It has been confirmed in a number of studies that mepolizumab, used by patients suffering from eosinophillic asthma, decreases the number of exacerbations and reduces systemic glucocorticoid doses. The approval of mepolizumab therapy to trading in Poland is regulated by provisions of the drug programme, discussed in detail further in this paper.

Introduction:

In recent years, one could observe a huge breakthrough in pharmacotherapy. It applies both to rare and very rare conditions, such as, for example, congenital angiooedema or the of recurrent fever syndrome, but also to many chronic diseases of severe course and with to-date's poor prognosis for affected patients. This therapeutic progress results, among others, from the launch of many biological medicines. Unfortunately, the costs of these therapies are usually very high, therefore, particular countries offer various types of reimbursement. In Poland, these expensive and innovative therapies are provided under the, so-called, drug programmes.

According to its definition, a drug programme is *„a guaranteed service, under which the treatment is carried out, using innovative, expensive active substances which are not funded under other guaranteed services. Such a treatment is carried out in case of selected conditions and targets an accurately defined group of patients."* It means that only these patients are qualified to these therapies, who meet specific inclusion and exclusion criteria (similarly as in clinical trials), defined in program specifications, and the treatment is provided exclusively by specialists with experience in biological therapies. It should enable a better qualification of patients and, thereby, a more efficient use of financial means.

Asthma is one of chronic diseases with a high incidence rate. It requires continuous therapy which should lead to remission of symptoms, decrease the risk for exacerbations or suppress the development of distant complications with a simultaneous low danger of adverse effects. A successful therapy ensures most often a good or very good asthma control. It is, however, estimated that 5 to 10% of patients are resistant to standard treatment.[1] There are various reasons for this resistance, whereas steroid dependence, as well as relative steroid resistance, are commonly observed in these patients, who often require a systemic glucocorticosteroid therapy, vitiated by numerous adverse effects. Studies to achieve an efficient control of asthma have been underway for many years also in these patients, what would reduce the number of exacerbations, emergency visits or hospitalisations. A first step in this direction was the perception of asthma as not only a single medical condition, characterised by a chronic inflammatory state but as a heterogeneous syndrome (this term was for the first time introduced in the GINA 2014 document).[2] Various phenotypes of asthma began to be identified - at first, on the basis of clinical course or dominating cellularity in inflammatory infiltration (e.g., neutrophilic, eosinophilic or low granulocyte asthma). Further divisions resulted from performed cluster analyses. The primary objective of phenotyping was an identification of the pathomechanism which was dominating in a specific group of patients with asthma, which should have, in turn permitted a launch of a more efficient, individualised therapy, targeting that specific pathomechanism. That new perception of asthma opened the way to entirely new medicinal products. Omalizumab (XOLAIR®) was the first biological product to be used in asthma therapy (its approval to trading at the European Union has been valid since 25th October 2005). Following its summary of product characteristics (SmPC), omalizumab is "indicated as adjunctive treatment for asthma control in patients with severe, chronic allergic asthma and with confirmed positive skin patch test results or with *in vitro* reactivity to perennial aeroallergens".[3] Allergic asthma accounts for approximately 40% of severe asthma cases. It is assumed that IgE immunoglobulins are of key importance for the development of allergic inflammation. This activity depends on IgE binding with the specific receptor of high affinity (FcεRI), which occurs in mastocytes and basophils, as well as an attachment of these antibodies to CD23 molecules on the surface of lymphocytes B and of antigen presenting cells. Omalizumab is a humanised antibody oriented against IgE. So far it has been taken as a paradigm that the drug binds only free, unbound antibodies, precluding their binding with the receptor and thus leading to suppression of inflammatory reaction. The recent studies, however, demonstrated that omalizumab also affects the dissociation of IgE molecules, already bound with receptors on mastocytes and basophils, what additionally enhances the drug action.[4] It has been observed that, following 16-24 weeks of therapy, the free IgE level does not exceed 89-98% of its baseline value. This drop results in a down regulation of the FcεRI expression on mastocytes and ba-

sophils.[5,6] The significant therapeutic efficacy, as well as the safety of omalizumab treatment, has been confirmed in many studies, involving patients with the phenotype of allergic asthma.[7,8,9] This therapy has been available in Poland since March 2013 under the "Treatment of severe, allergic, IgE-dependent asthma with omalizumab" drug programme.[10]

Eosinophilic asthma:

Eosinophilic asthma is another phenotype of the disease and the subject of this work. Eosinophilic asthma is characterised by raised levels of inflammatory Th2 markers, such as interleukins: IL-4,-5 and 13. The clinical features of this type of asthma include its late onset (rarely in childhood) and the rather rapid progression towards its severe form from the time point when the first symptoms occur, while affected patients often require the use of systemic glucocorticosteroids. It is a group of patients in whom atopic features are more rarely identified, while eosinophilia is found in blood and tissues demonstrate eosinophilic infiltrations. High FeNO levels are also observed. Severe asthma of this phenotype is often accompanied by chronic rhinosinusitis with nasal and sinus polyps. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is also occasionally observed.[11,12,13] Eosinophils are regarded to be cells of major significance in the pathogenesis of asthma for their effects, are exerted onto many other cells of the immune system, which take part both in congenital and acquired immunity. Interleukin 5 (IL-5) demonstrates a significant effect on the proliferation and maturation of bone marrow and on the activation of eosinophils at inflammation site; IL-5 is also simultaneously considered to be the only eosinophil-poietic factor. It is the reason why IL-5 has been selected to be a therapeutic goal in severe eosinophilic asthma. As a consequence, it has been assumed that a block of its function could inhibit the formation of eosinophilic infiltrations, thus providing an optimal target for biological therapies.

Currently, two IL-5 blocking mechanisms are used. The first one (with Mepolizumab (NUCALA®) and Reslizumab (CINQAERO®)) consists of an uptake of circulating interleukin by specific antibodies. The bounded IL-5 is not able to be connected with the receptor, what leads to signal blocking. Both above-mentioned drugs have already been approved to trading in Europe.

The other mechanism (Benralizumab (FASENRA®)) is such that the drug is directly bound with subunit α of the receptor for IL-5 (RIL-5 α = CD125) and blocks IL-5 binding, however, an additional activity is very important, resulting from the structure of Fc fragment of benralizumab. The lack of fucose residue on the oligosaccharide core increases the affinity and enhances the binding force of the drug to the FcγRIIIa receptor (on NK cells, granulocytes and other cells), what brings about the phenomenon of antibody dependent cellular cytotoxicity (ADCC) and leads to apoptosis of target cells. Performed studies indicate that the administration of even a single dose of the medicine leads to a significant reduction of the number of eosinophils in the peripheral blood, sputum and the mucous/submucous membrane of the respiratory tract. A significant reduction in the number of basophils has also been observed with IL-5Rα receptor expression. The therapeutic effect of the drug on the number of exacerbations has clinically been confirmed (reduction by 51%) and on the dose of received systemic glucocorticosteroids (approximate dose reduction by 75% and total drug withdrawal in 52% of patients), as well as on the results of pulmonary functional tests (FEV1 increase by 159 ml vs. placebo). Benralizumab has already been approved by FDA to trading as an additional therapy in severe eosinophilic asthma treatment in adults and children till 12 years of age (approval date: 14th November 2017).[14,15,16]

Two IL-5 blocking drugs are now approved to trading in Europe: Mepolizumab and Reslizumab. Since the 1st November 2017, by the order of the Minister of Health, mepolizumab has become an available medicinal product also for patients in Poland, following the entry into force of the "Treatment of severe, allergic, IgE-dependent asthma (ICD-10 J45.0) and of severe eosinophilic asthma (ICD-10 J45)" drug programme.[17]

Mepolizumab is a humanised monoclonal antibody (IgG1, κ), oriented against human interleukin-5 (IL-5). It is characterised by high affinity and specificity. The drug is subcutaneously administered, in the upper part of the arm, in the thigh or the abdomen, its dose being constant, regardless of body mass: 100 mg s.c., every 4 weeks. The approved indications encompass adult patients with severe, treatment-resistant eosinophilic asthma. In the studies, presented below, it was proven that mepolizumab was efficient in the treatment of patients with severe eosinophilic asthma: the administration of the medicine led to a significant reduction in the number of exacerbations, controlled the number of eosinophils and significantly reduced the dose of systemic glucocorticoids (by approx. 50%).

In the **DREAM (Dose Ranging Efficacy and Safety with Mepolizumab)** study with i.v. mepolizumab administration, it was attempted for the first time to define the phenotype of asthma, associated with a good response to anti-IL-5 treatment, as well as to determine the most efficient and safest dose of the drug.[18] A group of 621 patients with severe, recurrent exacerbations of asthma with eosinophilic inflammation (eosinophilia in sputum

and in peripheral blood, increased FeNO) were randomly (1:1:1:1) assigned to groups, receiving various doses of mepolizumab (75 mg, 250 mg, 750 mg) or placebo (a total of 13 doses in 4-week intervals). That group was additionally stratified with regards to reception or not of oral glucocorticosteroids. The obtained results did confirm that mepolizumab considerably reduced the number of exacerbations in the group of patients with eosinophilic asthma in comparison with placebo. Significant effects were also exerted on eosinophilia in peripheral blood and sputum, regardless of received dose. What is interesting, the risk of asthma exacerbation significantly decreased notwithstanding the only slight effect of the therapy on the traditionally used markers of asthma control: FEV1 and scores in Asthma Control Questionnaires (ACQ) and in the Asthma Quality of Life Questionnaire (AQLQ). It was accepted that such a discrepancy between the symptoms and the risk of exacerbation was typical for patients with severe asthma. A performed cluster analysis confirmed that symptoms and the risk exacerbations were entirely distinct, mutually unrelated features. This clear separation of daily symptoms from the risk of asthma exacerbations entails significant consequences for the ways of asthma assessment and control in particular subgroups of affected patients. It also means that various aspects of the disease require a different therapeutic approach. Consequently, patient evaluation should also be differently performed in clinical studies. A large group of patients, involved in the DREAM study, as well as the comparable effect of the therapy, clearly independent of mepolizumab dose, enables a reliable evaluation of the basic variables, associated with the response to treatment. It was revealed that merely two parameters influenced the therapy efficacy: the baseline number of eosinophils in peripheral blood and the prevalence of exacerbations in the preceding year. An important conclusion from the DREAM study was that an identification of a target population to be treated with mepolizumab - perhaps also with other biological medicinal agents - could require a differentiated definitions and concept of the disease itself, as well as the application of still insufficiently identified and understood biomarkers.

The DREAM study enabled to find out an efficient therapeutic dose and describe the patient's profile which should be responsive to mepolizumab therapy. Therefore, in the subsequent study, designated by the acronym of MENSA (mepolizumab as adjunctive therapy in patients with severe asthma)[19], the qualified patients included only those with confirmed eosinophilia in peripheral blood, a high exacerbation incidence rate, demanding the use of oral glucocorticosteroids (a minimum of 2 in the previous years) and receiving a high dose of inhaled glucocorticosteroids (a minimum of 880 μg, when converted into fluticasone propionate). The MENSA study involved a total of 576 patients with severe eosinophilic asthma (eosinophilia in peripheral blood at 150/μL in screening or 300/μL at any time point in the previous year), uncontrolled despite the reception of steroids and glucocorticosteroids in high inhaled doses (a part of the patients), who were randomly assigned to the following groups: mepolizumab in i.v. 75 mg doses, mepolizumab in s.c. 100 mg doses and placebo. The drug was administered in 28-day intervals for 32 weeks. The primary objective of the MENSA study was an answer to the question whether any therapy with the use of antibodies against interleukin-5 could reduce the necessity of a frequent administration of systemic glucocorticosteroids in patients suffering from severe asthma, the majority of whom did not require a chronic reception of the medicinal agents. The results of the study confirmed a significant effect of the therapy on the number of exacerbations, which was reduced by 47% in the group with i.v. mepolizumab administration and by as much as 53% in the group with s.c. mepolizumab administration vs. placebo. In the 32nd week, the mean value of FEV1 - vs. the baseline study - was higher by 100 ml and 98 ml in the group with i.v. and s.c. mepolizumab administration, respectively, than in the placebo group. In addition, the number of exacerbations, demanding an emergency intervention or hospitalisation in the above-mentioned groups with mepolizumab administration was 9% and 6%, respectively, while being 13% in the placebo group, what corresponds to a reduction in the incidence rates of severe exacerbations in the patients, treated intravenously and subcutaneously with mepolizumab by 32% and 69%, respectively. Unlike in other studies, both AQLQ and ACQ indicators were improved in the mepolizumab treated group with their 32-week increase recorded already after the 4th week from the therapy onset. The other assessed parameter, i.e. eosinophilia in peripheral blood, also considerably decreased in the verum group, where the highest drop (by 83% and 86% in the i.v. and s.c group, respectively) was observed after 12 weeks of the therapy. The decrease maintained also in subsequent weeks of the study.

A common analysis of the above-mentioned studies, the goal of which was to find out a relationship between the baseline number of eosinophils and the efficacy of the therapy with mepolizumab, revealed a close correlation between eosinophilia in peripheral blood and the response to treatment: a clinically significant decrease in the number of exacerbations was observed in the patients with the baseline number of eosinophils equal to or higher than 150 cells/μL. Eosinophilia in peripheral blood may then be approached as an auxiliary marker to be used in the qualification of patients in whom mepolizumab therapy should bring about effective outcomes.[20]

It was not checked, either in the DREAM study or the MENSA study, if mepolizumab exerted any saving influence on the dose of orally received glucocorticoids. Such

an evaluation was carried out in the SIRIUS (Steroid Reduction with MepolizUmab Study)[21], the goal of which was to find out the effects of mepolizumab treatment on reduction of oral glucocorticosteroid doses. A total of 135 patients with severe asthma and eosinophilia in peripheral blood (300 eosinophils/μL within 12 months before inclusion to the study or 150/μL in the optimisation phase), persisting despite an administration of systemic glucocorticosteroids (5-25 mg of prednisone or another steroid in an equivalent dose). The patients were randomly assigned to one of two groups and received mepolizumab in s.c. 100 mg doses or placebo (1:1) for 20 weeks in 28-day intervals. The doses of systemic glucocorticosteroids were simultaneously reduced every 4 weeks, monitoring asthma control and symptoms of adrenocortical insufficiency. At the end of the study, a significant reduction of the systemic glucocorticoid dose was observed in the mepolizumab group, where the chance to decrease the steroid dose was 2.39 times higher in those patients than in the placebo group, with the mean dose reduction reaching 50%. Similarly as in other studies, there was a favourable influence of mepolizumab on the number of exacerbations, asthma control and the quality of life with a simultaneous, clinically significant reduction of the oral dose of glucocorticosteroids. A similar dose saving effect of mepolizumab on systemic glucocorticosteroids was observed in a small, pilot study of Nair et al.[22] In that study, 20 patients with severe asthma and enhanced induced eosinophilia in sputum (>3% despite the use of systemic glucocorticosteroids) were administered mepolizumab or placebo in i.v. 750 mg doses every 4 weeks for 20 weeks. The therapy allowed to reduce the dose of prednisone by 84% in the mepolizumab group vs. 48% in the placebo group. A similarity of results in the SIRIUS and Naira studies suggests that the presence of eosinophils in peripheral blood is a sufficient criterion to qualify patients to treatment. It confirms also that the efficacy of mepolizumab therapy is independent of the route of administration.

Powell et al. carried out a metaanalysis in 2015, the goal of which was a comparison of mepolizumab and placebo effects on exacerbations and the quality of life of adults and children with asthma.[23] The metaanalysis encompassed 8 clinical studies with the total number of 1707 subjects. Children at the age above 12 years of life participated in two of the above-mentioned studies but, since the results, obtained in those two groups were not separately presented, it was not possible to draw up any specific conclusions, regarding the therapeutic effects particularly in children. The major limitation and cause of errors in the analysis was a considerable differentiation of inclusion criteria, taking into account the severity and clinical course of asthma. The studies involved both patients with mild/moderate atopic asthma and those with severe eosinophilic asthma with recurrent exacerbations. A clinically significant reduction of the exacerbation rate was demonstrated in two studies, regarding the groups of patients with eosinophilic asthma. Whereas an analysis of 4 studies, where the study group was not limited to asthma with eosinophilia, demonstrated significant heterogeneity and a lack of any significant differences regarding exacerbations. The authors of the discussed metaanalysis emphasise the fact that no unequivocal conclusions may be drawn up from it with regards to the significance of mepolizumab therapy of patients with asthma, although the therapy seems to favourably influence the quality of life and reduce the incidence of exacerbations in patients with severe eosinophilic asthma. The authors also highlight a necessity of further clarifying investigation to find out which subgroups of patients with asthma could potentially benefit from the treatment.

Drug programme:

The outcomes of clinical studies, confirming the efficacy and safety of mepolizumab therapy, resulted in a marketing authorisation, issued in December of 2016. This medicinal agent has also become available in Poland since 1st November 2017. However, taking into account the fact that reimbursement is provided under the framework of drug programme, patients have to meet strict inclusion criteria. Following these criteria (Table 1), the treatment with mepolizumab may include exclusively adult patients with diagnostically confirmed severe eosinophilic asthma, characterised by the number of eosinophils ≥ 350 cells/μ, uncontrolled and classified at STEP 4 acc. to GINA (Global Initiative for Asthma), in whom at least 2 exacerbation events occurred during the year, preceeding the inclusion into the programme, which required the introduction of systemic glucocorticoids or an increase of their dose in case of patients with chronic use of glucocorticosteroids, for a period longer than three days, with FEV1 < 80% and with symptoms of uncontrolled asthma. The introduction of the therapy is possible under the condition of exclusion of other hypereosinophilia syndromes, as well as of parasite infection and of other, clinically significant pulmonary diseases. The therapy should be terminated if no strictly defined asthma control improvement (Table 1.) is achieved at the specified control time points (after 24th, 52nd and 104th week). The evaluation includes, first of all: the number of exacerbations, the improvement of asthma control and of the quality of life (ACQ and AQLQ questionnaires and an evaluation of the response to therapy, carried out by the attending physician acc. to the GETE (Global Effectiveness Treatment Evaluation) scale). The results of the evaluation have to be either very good (total asthma control) or good (significantly improved asthma control). At every visit with mepolizumab administration, spirometry or PEF is requires, as well as questionnaires are filled in, evaluating the quality of life and disease control.

Unlike in case of the treatment with omalizumab, where the physician decides about therapy termination, the provisions of the drug prescription programme for mepolizumab limit the therapy duration period to 24 months. After this period of time, the therapy has to be suspended in each particular case for a minimum of 6 months. During this mepolizumab withdrawal period, the patient has to be followed up with regards to asthma control (at appointments, repeated every 4-6 weeks), so that the patient is able to receive the medicine immediately if a significant exacerbation of the disease occurs.

Table 1. Inclusion criteria, contraindications for mepolizumab and exclusion criteria in the mepolizumab therapy programme in severe eosinophilic asthma.[17]

Inclusion criteria:

1. patients above the 18th year of life with severe, treatment resistant eosinophilic asthma, identified by the number of eosinophils in blood at the level of ≥350 cells/μl, either at a qualifying visit or within 12 months, preceding the patient's qualification to participation in the programme;
2. the necessity of using high inhaled doses of glucocorticosteroids (>1000 mcg of beclomethasone dipropionate daily or another inhaled glucocorticosteroid in an equivalent dose), in combination with another asthma controlling drug (a long-acting agonist of β-2-adrenergic receptor, a leukotriene modifier, a theophylline derivative or a long-acting blocker of muscarinic receptor);
3. two or more exacerbation episodes during the recent year, requiring to apply systemic glucocorticosteroids or to increase their dose for a period longer than three days in patients on chronic glucocorticosteroid therapy, demanding or not hospitalisation or a visit at a hospital emergency department;
4. forced expiratory volume in 1 second (FEV1) < 80% of normal level before the administration of a bronchodilating drug at a qualifying visit;
5. symptoms of uncontrolled asthma (no asthma control in the Asthma Control Questionnaire (ACQ)>1.5) and asthma-related life quality deterioration (the mean AQLQ (Asthma Quality of Life Questionnaire) score < 5.0), despite applied therapy;
6. exclusion of other hypereosinophilia syndromes;
7. patient's non-smoking declaration;
8. exclusion of parasite infection, based on normal stool result;
9. exclusion of other clinically significant pulmonary diseases.

Contraindications to mepolizumab therapy:

1. hypersensitivity to mepolizumab or excipients;
2. pregnancy;
3. breast feeding;
4. concomitant therapy with immunosuppressive drugs, anti-cancer drugs, infusions from immunoglobulins and therapy with other biological medicines;
5. an intake of other biological medicines in the therapy of asthma (e.g., omalizumab) - till 6 months from therapy termination.

Exclusion criteria:

1. the occurrence of asthma exacerbations (defined as in 2.1. 3) during mepolizumab therapy, their number being equal or higher from that, observed during the year before therapy;
2. in patients who - before mepolizumab therapy - were on chronic therapy with systemic glucocorticosteroids (continued for a minimum of 6 months), when either no dose reduction or dose reduction by <= 30% was observed;
3. an evaluation of the response to therapy, carried out by the attending physician acc. to the GETE (Global Effectiveness Treatment Evaluation) scale, lower than very good (total asthma control) or good (significantly improved asthma control);
4. no improvement of asthma control in the Asthma Control Questionnaire (ACQ increase by > or = 0.5 (in comparison with that, recorded at the patient's qualification visit, regarding mepolizumab therapy);
5. no improvement of the quality of life in the Asthma Quality of Life Questionnaire (AQLQ drop by > or = 0.5 (in comparison with that, recorded at the patient's qualification visit, regarding mepolizumab therapy);
6. patient smoking;
7. non-compliance with doctor's recommendations or with prescribed therapy regimens;
8. the onset of therapy with immunosuppressive drugs, anti-cancer drugs, immunoglobulins infusions and therapy with other biological medicines;
9. the occurrence of any contraindications to mepolizumab therapy:
10. pregnancy;
11. in case of resistant to treatment parasite infection - suspend mepolizumab therapy until the infection is cured.

Comments to the provisions of the drug prescription programme - the part applying to mepolizumab therapy in severe eosinophilic asthma:

Many years of experience with omalizumab therapy, which became available in March of 2013, as well as a review of reports from performed studies, enable a critical view of the actual provisions of the programme.

Inclusion criteria:

Item 1) patients may be included (...) with severe, treatment resistant eosinophilic asthma, identified by the number of eosinophils in blood at the level of ≥350 cells/µl.

The available evaluations[20] show that the threshold value of eosinophils, significant for patients, i.e. such at which a patient benefits from treatment, is ≥150 cells/µl. It seems then that the narrowing of the group of patients to those with the number of eosinophils ≥350 cells/µl may restrict the access to treatment for many patients, especially that systemic glucocorticosteroids, which are very often chronically used by these patients, may significantly reduce the number of these cells in peripheral blood.

Item 6) Exclusion of other hypereosinophilia syndromes (HES)

It appears from this approach that eosinophilic asthma belongs to hypereosinophilia syndromes (exclusion of **other** hypereosinophilia syndromes), whereas according to the applicable definition: "The hypereosinophilic syndrome (HES) is a co-occurrence of HE (≥1500 cells/µl) and of abnormal functions or damage of organs caused by eosinophilic infiltrations". It appears from the definition that the term of hypereosinophilic syndrome should not be used when hypereosinophilia is the only symptom in a given patient. There are also other conditions which do not belong to HES, where HE is also one of the symptoms. These conditions include, e.g., EGPA (eosinophilic granulomatosis with polyangiitis, otherwise known as Churg-Strauss syndrome) and certain immunity disorders. Despite often significant eosinophilia and organ infiltrations, these are not conditions falling into the HES. There is also a fairly large group of diseases, accompanied by eosinophilia, while its significance remains unknown. These are, for example, connective tissue disorders with vascular involvement, sarcoidosis, colitis ulcerosa, HIV infection or the hyper IgE syndrome. There are also syndromes in which organ restricted infiltrations are the primary problem, however with concomitant peripheral eosinophilia, as well as eosinophilic disorders of the gastric tract, chronic eosinophilic pneumonia or Wells syndrome.

Summing up: one should expect a more precise specification of how hypereosinophilic syndromes are defined by the payer and what examinations / tests should be obligatory at which level of eosinophilia. It may, among others, allow to find out whether, in the light of the provision, for example, the Churg-Strauss syndrome is an exclusion criterion from mepolizumab therapy in line with the applicable drug prescription programme.

Item 8. Exclusion of parasite infection, based on normal stool result - in the provision, concerning diagnostic examinations, required by the programme, there is a phrase: "diagnostic examinations to exclude parasite infections". The plural number, applied in this phrase, would indicate that, at least, two examinations/tests are necessary. In the publications, concerning parasite infections (also Polish)[25], the lack of a golden standard is emphasised in the diagnostics of parasite infestations, what is associated with a rather big methodological diversification in this particular respect.

Summing up: it is necessary to determine more precisely which examinations / tests are specifically required by the payer as a screening package towards parasite infestations, applicable for all candidates to the mepolizumab therapy programme.

Exclusion criteria:

Item 2) in patients who - before mepolizumab therapy - were on chronic therapy with systemic glucocorticosteroids (continued for a minimum of 6 months), when either **no dose reduction or dose reduction by <= 30% was observed**;

Taking into account the results of studies (e.g. SIRIUS) (24), one may estimate that in 25% of patients, systemic glucocorticoid dose reduction will not be possible (a similar experience was gained in our studies in patients treated with omalizumab (unpublished data)), whereas in this group of patients, systemic glucocorticoid dose reduction will not be possible for reasons other than the lack of asthma control, such as, for example, too short time period to the first follow up visit but also symptoms of adrenocortical insufficiency, precluding dose reduction or complete withdrawal of systemic glucocorticoids. According to the actual provisions of the programme, the patient will have to be, in such a case, excluded despite, for example, a simultaneously observed asthma control improvement, better quality of life or higher scores of treatment efficacy in the GETE scale.

Therapy time period in the programme.

The actual provision does not allow the therapy to be continued for a period longer than 24 months - in every

case, the therapy has to be suspended and the treated patient submitted to follow up.

There are currently no studies which could enable to assess how long mepolizumab therapy should last. It can be reasonably assumed that, since this medicinal product has been present on the market for 2 years, the first publications should soon be published. concerning clinical experiences with the use of this agent, including post-therapy evaluations of patients at follow up stages. The actual provisions does not enable the doctor to carry on the therapy, even if the drug withdrawal after 24 months may turn out to be premature and lead to quick recurrence of symptoms. The provision, concerning omalizumab treatment, is much safer for the patient as it is the attending physician who decides when the therapy should be terminated.

Diagnostic examinations and tests in the programme.

Item 1) spirometry or PEF, if there are contraindications to spirometric test.

Based on the experience, gained from the therapy with omalizumab, we are aware of rather frequent situations when the patient is not able to perform a spirometric test (e.g. eye surgery). Therefore, it is good that currently the system offers in such situations a possibility to replace such a study by an easier PEF measurement.

Item 7) fractional exhaled nitric oxide (FENO)

A single FENO test does not determine the onset of mepolizumab therapy (it is not an inclusion criterion). Neither is it a parameter to be used in monitoring the course of asthma (the test is run only once as part of patient's qualification procedure). Neither is the test recommended by the applicable standards for asthma diagnostics and therapy (GINA 2017)[2], which emphasise the low value of the test, associated with the fact that the measure parameter may rise also in the course of conditions other than asthma, such as eosinophilic bronchitis, atopy, allergic rhinitis or eczema. The FeNO parameter may also increase in asthma of the type other than eosinophilic (e.g., in neutrophilic asthma). Besides, the level of nitric oxide in exhaled air is also determined by many other factors: it is decreased in smokers but also during bronchospasms and in early allergic reactions.

If we add to this the unavailability of the device at many specialised centres, imposing the necessity to purchase the equipment exclusively for the needs of the drug programme, it seems that this provision of the programme should either be erased as soon as possible or the payer should take into account a possible failure of its execution.

Summary:

The reimbursement policy under the drug programme for innovative therapies in Poland allows for administration of medicinal products which are effective and safe in the therapy of severe asthma. It applies, first of all, to omalizumab, a medicinal agent, used already for 5 years, which ensures effective therapy for patients with allergic asthma. However, this therapy is not possible in a fairly large group of patients for the lack of atopy. There are many patients in this group suffering from severe eosinophilic asthma. Mepolizumab is a chance for them - being reimbursed in Poland since 1st November 2017 under the drug programme. The therapeutic efficacy of this agent has been confirmed in many studies. We shall soon gain our own experiences, associated with the use of the agent.

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