ZIOJŁA-LISOWSKA, Kinga, KUZIO, Agnieszka and CIEPLIŃSKA, Aleksandra. Treatment of COPD with a particular focus on biological therapy: a systematic review. Quality in Sport. 2024;17:53022. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.17.53022
https://apcz.umk.pl/QS/article/view/53022

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.07.2024. Revised: 15.07.2024. Accepted: 17.07.2024. Published: 19.07.2024.

Treatment of COPD with a particular focus on biological therapy: a systematic review

Leczenie POChP ze szczególnym uwzględnieniem leczenia biologicznego: praca przeglądowa

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Abstrakt

Wprowadzenie i cel. Przewlekła obturacyjna choroba płuc (POChP) jest heterogennym schorzeniem, które charakteryzuje się utrzymującymi się objawami ze strony układu oddechowego. Objawy te mogą znacząco obniżyć jakość życia chorych. Celem pracy jest

przegląd opublikowanego piśmiennictwa, dotyczącego leczenia POChP ze szczególnym uwzględnieniem roli leczenia biologicznego.

Metody przeglądu. Do wyszukiwania literatury wykorzystano internetowe bazy danych. Wszystkie wyszukane artykuły poddano analizie. Do przeglądu użyto głównie literatury opublikowanej po 2016 roku.

Opis stanu wiedzy. Konwencjonalne leczenie farmakologiczne chorych na POChP opiera się w głównej mierze na stosowaniu leków rozkurczających oskrzela. Stosuje się także glikokortykosteroidy (GKS). W ostatnim czasie coraz większą uwagę badaczy przykuwa możliwość zastosowania leczenia biologicznego w POChP. Największe nadzieje związane są z szerszym wykorzystaniem tych leków u pacjentów ze zwiększoną liczbą eozynofilów. Jednym z punktów uchwytu jest szlak IL-33/ST2, który częściowo kieruje procesami zapalnymi i remodelującymi w POChP - leki należące do tej grupy to tozorakimab, itepekimab, astegolimab. Innym szlakiem działania leków biologicznych jest blokowanie IL-5 - środki działające w tym mechanizmie to mepolizumab i benralizumab. Dupilumab jest przeciwciałem monoklonalnym, które ze względu na obiecujące wyniki badań, ma aktualnie największe szanse na rozszerzenie wskazań do leczenia POChP.

Podsumowanie. Podsumowując, jako że leczenie biologiczne daje nadzieję na możliwość lepszej kontroli choroby u szczególnych grup pacjentów, konieczne jest prowadzenie dalszych badań klinicznych w kierunku zastosowania leczenia biologicznego, które może wpłynąć na poprawienie jakości życia osób z POChP, szczególnie słabo reagujących na konwencjonalne leczenie.

Keywords. POChP, przewlekła obturacyjna choroba płuc, leczenie biologiczne

Abstract

Incroduction and aim. COPD is a heterogeneous condition characterized by persistent respiratory symptoms. These symptoms can significantly reduce the quality of life for patients. The conventional treatment used so far is not always effective, especially in cases of severe disease and in specific phenotypes, which is why researchers are constantly searching for new drugs. The aim of this paper is to review the published literature on the treatment of COPD, with particular emphasis on the role of biological therapy.

Material and methods. Online databases were used for literature research. The review primarily included literature published after 2016.

Analysis of the literature. Conventional pharmacological treatment for COPD patients mainly relies on the use of bronchodilators. Recently, researchers have increasingly focused on the potential use of biological therapy in COPD. The greatest hope lies in the broader use of biological therapy in patients with COPD with elevated eosinophil counts. One of the targets is the IL-33/ST2 pathway, which partially directs inflammatory and remodeling processes in COPD. Drugs belonging to this group include tozorakimab, itepekimab, and astegolimab. Another mechanism of action for biological drugs is blocking IL-5; drugs that work through this mechanism include mepolizumab and benralizumab. Dupilumab is a monoclonal antibody that, due to promising research results, currently has the greatest potential for expanding indications for the treatment of COPD.

Conclusion. Since biological therapy offers hope for better disease control in specific groups of patients, further clinical research is necessary to explore the use of biological treatment. This could improve the quality of life for individuals with COPD, especially those who respond poorly to conventional treatment.

Keywords. COPD, chronic obstructive pulmonary disease, biology treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by persistent respiratory symptoms and airflow obstruction.[1] COPD is the third leading cause of death worldwide.[2] It is estimated that around 384 million people globally struggle with this disease,[3] and in Poland, it may affect around 2 million people, with probably only about 20% of them being diagnosed and treated.[4] The most common cause of COPD is tobacco smoking (both active and passive), along with exposure to other harmful gases, dust, and air pollution, leading to chronic inflammation of the respiratory tract mucosa.[5] This manifests as chronic shortness of breath, mucus retention in the airways, cough with sputum production, and reduced exercise tolerance.[4] These symptoms can significantly lower the quality of patients' lives, making it essential to early detect and initiate appropriate treatment aimed at improving quality of life, achieving optimal symptoms control, preventing exacerbations, and treating comorbidities.[6,7] A healthy lifestyle, particularly quitting smoking, is crucial in COPD

treatment as it has the most significant impact on the natural course of the disease.[8] The foundation of pharmacological treatment is the use of inhaled bronchodilators from the beta2-agonist group, anticholinergic drugs, and inhaled corticosteroids. However, such treatment does not always yield satisfactory results and may not achieve adequate symptom and exacerbation control. Therefore, new treatment methods based on biological drugs have been developed, offering hope for improved quality of life for COPD patients in the future. The aim of this paper is to review the published literature on the treatment of COPD, with a particular focus on the role of current biological treatments and the potential for their broader use in the future.

Material and methods

Literature was searched using online databases such as PubMed and Google Scholar. Articles were searched using keywords in both Polish and English, such as "COPD treatment", "biological treatment in COPD" and the names of individual biological drugs were also entered. The website euclinicaltrials.eu was used to obtain up-to-date information on the phases and progress of clinical trials. The retrieved articles were analyzed. The review primarily used literature published after 2016.

Analysis of the literature

Conventional treatment, GOLD

An important source of knowledge about COPD treatment are the reports published by The Global Initiative for Chronic Obstructive Lung Disease (GOLD). The 2023 update (published in November 2022) includes several significant changes in the classification and treatment of COPD. The key change is the replacement of the previous four categories (ABCD) with three categories (ABE), where group E is a combination of groups C and D. Group A includes individuals with low risk of exacerbations and low severity of symptoms, group B includes individuals with low risk of exacerbations and high severity of symptoms, and group E includes individuals with high risk of exacerbations regardless of symptom severity.[9] The pharmacological treatment of COPD patients is primarily based on the use of bronchodilators, as presented in Table 1.[7,9]

Long-acting beta2-adrenergic receptor agonists (LABAs)	Formoterol
	Salemeterol
Short-acting beta2-adrenergic receptor agonists (SABAs)	Salbutamol
	Fenoterol
Long-acting anticholinergic drugs	Tiotropium
Short-acting anticholinergic drugs	Ipratropium bromide

Table 1. Bronchodilators[7,9]

In group A, it is recommended to use LABA or LAMA, in group B LABA + LAMA, and in group E LABA + LAMA + inhaled corticosteroid (ICS) if the number of peripheral eosinophils is >300. Triple therapy (with ICS) is also recommended for patients taking LAMA + LABA with eosinophil count >100 and experiencing exacerbations, as well as for those treated with monotherapy with eosinophil count >300 and experiencing exacerbations.[7]

Regarding the use of inhaled corticosteroids in COPD patients, there are both advantages and disadvantages.[7,10] These medications are included in COPD treatment algorithms in specific situations mentioned above and in cases of coexisting asthma. Although the latest GOLD report no longer includes the LABA + ICS regimen, it allows its continuation if previously initiated and if clinical outcomes are satisfactory.[7] The main risk associated with chronic ICS use is an increased risk of pneumonia, which can be severe in COPD patients; therefore, the use of these drugs requires an analysis of potential benefits and harms in each case.[7,10]

Another medication used in COPD treatment is roflumilast, a selective phosphodiesterase-4 (PDE4) inhibitor. This drug has anti-inflammatory effects, including reducing the number of inflammatory mediators released by neutrophils and decreasing the release of pro-inflammatory cytokines. It is mainly used in patients with FEV1 <50% and chronic bronchitis with exacerbations, who often have elevated inflammatory markers.[7,11]

Biological treatment in COPD

In most cases, airway inflammation in COPD is caused by a Th1-dependent response, which is associated with an increased number of neutrophils. However, in some cases, there is a mixed response or a Th2-type response, which is associated with Th2 lymphocytes, eosinophilia, and ILC2 cells.[12] ILC2 cells actively participate in the development of allergic reactions. These cells are stimulated by alarm cytokines - IL-33, IL-25, and TSLP - released by the damaged respiratory epithelium, in response to which ILC2 cells secrete IL-4, IL-5, IL-9, and IL-13, leading to increased mucus production, cell migration, and the development of a full immune response.[13] Asthma is primarily an allergic disease mediated by the aforementioned cells and cytokines. This is why biological treatment with monoclonal antibodies has been successfully used in asthma for many years.[14] COPD is much less dependent on the mechanisms described above, which is why the use of biological drugs in this disease is not as common. However, studies conducted so far show that there is potential for applying these modern treatment methods to COPD as well.

IL-33 as a therapeutic target

There are several different biological drug targets being studied for use in the treatment of COPD which are presented in Table 2.[15,16,17]

Main target	**Drug**
IL-33	Tozorakimab
	Itepekimab
	Astegolimab
IL-5	Benralizumab
	Mepolizumab
TSLP	Tezepelumab
IL-4/IL-13	Dupilumab

Table 2. Main targets of the described biological drugs[15,16,17]

One of these is IL-33 - a cytokine from the IL-1 family produced, among other places, in the respiratory epithelium in a reduced form, which is then oxidized extracellularly and, in this

form, binds to the ST2 receptor. This receptor is found in the membranes of immune cells such as ILC2, mast cells, or endothelial cells and can also be induced on additional types of immune cells like NK cells.[15,16,17] Upon binding to ST2, IL-33 initiates the NF-kappaB nuclear factor signaling pathway and mitogen-activated kinase signaling.[16] This triggers a cascade of type 2 inflammatory responses, although there is evidence that IL-33 may also participate in type 1 inflammation.[16,18] IL-33 stimulates endothelial and lung epithelial cells to produce IL-6 and IL-8 cytokines, which cause neutrophil chemotaxis. These neutrophils damage the lungs by producing elastases and proteases, leading to fibrosis.[17] Studies have shown that dysregulated IL-33 activity may correlate with increased disease symptoms and lead to pathological inflammation and airway remodeling.[16,18] In COPD patients, elevated IL-33 levels in the blood correlate with a higher risk of exacerbations, and higher cytokine concentrations in lung tissue cause damage to alveolar epithelial cells.[19] Currently, there are ongoing studies on the potential use of three drugs targeting IL-33 in treating COPD patients.[17]

Tozorakimab is the first described monoclonal antibody that inhibits the action of IL-33, both in its reduced form by blocking the ST2 receptor and in its oxidized form by reducing signaling through a separate RAGE/EGFR pathway.[16,18] Therefore, tozorakimab's mechanism of action is different from other anti-IL33 antibodies that only work by blocking the IL-33-ST2 mechanism. Preclinical studies suggest that tozorakimab can reduce the number of eosinophils and the concentration of inflammatory biomarkers, including IL-5 and IL-13, in the blood of patients with mild airway obstruction.[16] The first phase clinical trial involving humans (NCT03096795) included healthy individuals and patients with mild airway obstruction. It demonstrated that the drug is safe, well-tolerated by patients, and has a linear, time-independent pharmacokinetic profile in serum with a low incidence of ADA (Anti-Drug Antibodies).[18] Currently, phase II studies (NCT04631016) are underway to assess its efficacy and safety in COPD and chronic bronchitis. Phase III studies are also ongoing to evaluate the effectiveness of various doses of tozorakimab in COPD patients with exacerbations despite optimal treatment.[17,19] The drug is also being investigated for potential use in several other diseases, such as asthma, acute respiratory failure, and diabetic kidney disease.[16]

Itepekimab is an another monoclonal antibody, belonging to the IgG4 class, and is directed against IL-33.[20] In studies conducted so far, itepekimab added to standard therapy has not significantly reduced the annual incidence of moderate and severe COPD exacerbations compared to placebo after 52 weeks of treatment. However, it reduced the frequency of

exacerbations and improved lung function in former smokers with COPD. Currently, two phase III studies (AERIFY 1 and 2) are underway to evaluate the drug's efficacy and safety in COPD patients, particularly comparing its effectiveness in reducing the number of exacerbations in the aforementioned group of former smokers with COPD compared to placebo.[17,20]

Astegolimab is a human monoclonal antibody that selectively binds to the ST2 receptor, inhibiting the interleukin 33 signaling pathway.[1] IL-33 is one of the substances released during allergic reactions.[3] For this reason, astegolimab was initially studied for use in asthma - studies showed that this drug reduces the frequency of asthma exacerbations in patients with severe asthma, even with low eosinophil counts.[21] However, it has not yet been proven to reduce the frequency of COPD exacerbations, but it has been shown to improve the overall health status of patients with moderate to very severe COPD compared to placebo. Further studies (phase II and III) are currently ongoing.[17]

Blocking the IL-5 pathway

Apart from IL-33, there are other potential targets for biological drugs in COPD. A certain group of patients with this disease have elevated levels of eosinophils in their blood and sputum. There is a correlation between this phenomenon and elevated levels of interleukin 5 in these patients.[17] IL-5 stimulates the growth, maturation, release, and survival of eosinophils, sustaining the inflammatory response.[12,14,22]

Benralizumab is a monoclonal antibody directed against the alpha subunit of the interleukin 5 receptor.[12,14] It has been shown that this drug, by blocking the IL-5 receptor on the surface of eosinophils, reduces the number of eosinophils in the blood, airways, and sputum by inducing their apoptosis through natural killer cells.[23] In a phase II study involving patients with moderate to severe COPD with eosinophilia, a reduction in eosinophil levels in sputum and peripheral blood was demonstrated, although there was no reduction in the risk of exacerbations.[12,24,25] The phase III GALATHEA/TERRANOVA clinical trials aimed to evaluate the efficacy of benralizumab as an additional chronic treatment for patients with frequent exacerbations of the disease despite treatment and with peripheral blood eosinophilia of at least 220/mm^2. The studies did not show a link between a reduction in the annual number of exacerbations and the use of benralizumab.[26] However, a post-hoc analysis of these studies demonstrated that benralizumab reduces the risk of moderate or severe COPD exacerbation

recurrence within 30 days (by 60% compared to placebo) and 90 days (by 42% compared to placebo) in patients who received the drug after an exacerbation. This effect was proven only in patients with high eosinophilia and previous frequent exacerbations despite optimized COPD therapy.[26]

Mepolizumab is a monoclonal antibody that has well-documented efficacy in reducing inflammation and the risk of exacerbations in people with severe asthma with elevated eosinophil levels in the blood and sputum. Therefore, the impact of mepolizumab on treating patients with severe COPD resistant to triple therapy with glucocorticosteroids and peripheral blood eosinophilia was investigated in the METREX/METREO study. Significant positive effects of mepolizumab were demonstrated in these patients - it reduced the frequency of moderate and severe exacerbations and extended the time between subsequent exacerbations. The treatment effect was better the higher the baseline eosinophil level was.[22,27] Despite these promising results, according to the authors Takudzwa Mkorombindo and Mark T. Dransfield[25], the benefits of the drug do not seem as advantageous as in asthma. Mepolizumab reduced the risk of exacerbations by 50% in severe hypereosinophilic asthma, whereas in COPD patients with hypereosinophilia, it was only 15%.[28] There is highlighted a greater heterogeneity of COPD exacerbation mechanisms compared to asthma, even among those with an eosinophilic phenotype - especially noting the particular role of older age and comorbidities, thus the effect of IL-5-targeted treatment may actually be smaller than expected.[25]

Other drugs

An interesting drug with a different mechanism of action is tezepelumab, an anti-TSLP antibody. TSLP is an epithelial alarm cytokine that primarily regulates the T2 immune response. This cytokine is produced, among other places, in the airways of COPD patients and may play a role in disease exacerbations.[17] Tezepelumab specifically binds to TSLP, thereby blocking its interaction with its heterodimeric receptor.[29] A phase II clinical trial is currently underway to evaluate the impact of tezepelumab in reducing airway inflammation in COPD patients, and a study assessing the drug's use as an adjunctive therapy to prevent COPD exacerbations was recently completed.[17]

Dupilumab is an antibody that binds to IL-4Rα and inhibits the release of IL-4 and IL-13 cytokines.[30] These cytokines are key mediators of the T2 inflammatory response.[31] Indications

for dupilumab include the treatment of asthma and atopic dermatitis, among others. The recently concluded phase III BOREAS study showed that the group of patients receiving dupilumab had better lung function, overall health, and lower exacerbation rates compared to placebo. These results were also confirmed in the NOTUS study, prompting the U.S. Food and Drug Administration to prioritize the evaluation of expanding indications to include COPD treatment, and the European Medicines Agency is also considering these indications.[12] According to the authors of a meta-analysis published in January 2024 on the safety and efficacy of biological treatments in COPD patients compared to traditional treatments, out of the eight drugs analyzed, only dupilumab significantly improved lung function by increasing FEV1.[32]

Conclusion

Chronic airway inflammation plays a crucial role in the pathogenesis of COPD, and there is still a lack of effective, targeted treatments that modify the main inflammatory response pathways.[33] Despite the fact that biological drugs are not yet approved for COPD treatment, there is hope that further research will identify the appropriate group of patients who could benefit from such treatment.[33] The greatest hopes are associated with the broader use of biological treatments in COPD patients with increased eosinophil counts.[34] One of the targets is the IL-33/ST2 pathway, which partially directs inflammatory and remodeling processes in COPD; however, the mechanisms of this action are more complex than in asthma, likely due to the greater heterogeneity of exacerbation mechanisms in COPD.[19] Another pathway for biological drugs is the blocking of IL-5 - both mepolizumab and benralizumab may have future applications in COPD treatment, but it is necessary to refine the patient groups that could potentially benefit from these drugs. Dupilumab is a monoclonal antibody that, due to promising research results, currently has the best chance of having its indications expanded to include COPD treatment. In summary, further clinical research is needed on the use of biological treatments, which may improve the quality of life for people with COPD, especially those who respond poorly to conventional treatment.

Declarations

Funding

No financial support was received by any of the authors for the manuscript preparation.

Conflics of interests

The authors declare no conflict of interest.

Author contributions

Conceptualization, K.Z-L.; Methodology, K.Z-L, A.K., A.C.; Investigation, K.Z-L, A.K., A.C.; Resources, K.Z-L, A.K., A.C.; Data Curation, K.Z-L, A.K., A.C.; Writing – Original Draft Preparation, K.Z-L, A.K., A.C.; Writing – Review & Editing, K.Z-L, A.K., A.C.; Visualization, K.Z-L.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data avalability

Not applicable.

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