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THE ROLE OF IMMUNOMODULATORY PREPARATIONS IN ASTHMA TREATMENT

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1. SUMMARY

Asthma remains one of the most prevalent respiratory tract disorders. The disease affects both adults and children and remains the most common cause of respiratory morbidity. Considering its significant impact on patients' quality of life and the treatment burdened with side effects, new therapy approaches affecting the clinical course of asthma are needed. Here we describe the current results that have been obtained on using immunomodulatory preparations in asthma. The analysis of previously published studies was conducted by using the PubMed and Scopus databases.

Probiotics, bacterial lysates (BLs), and pidotimod are immunomodulatory compounds affecting both adaptive and innate immunity. The therapy based on probiotics might modulate the intestinal microbiota and regulate the inflammatory response. Bacterial lysates promote immune response by reversing Th1/Th2 unstable balance, which leads to reduction of

allergen-induced airway hyperresponsiveness during asthma exacerbations. Pidotimod stimulates PRRs and increases the release of antimicrobial peptides which also leads to the improvement in the rate of respiratory tract infections. Some studies showed the beneficial effect of described preparations in asthma course. Regrettably, findings do not correspond with each other and the data referring to immunomodulatory compounds is still limited, thus there is an urgent need to conduct more, large sample studies.

The conclusion we can only draw is that immunomodulatory compounds may offer an alternative approach for symptom reduction and prophylaxis against both infections and exacerbations of asthma.

Key words: asthma; immunomodulatory compounds; bacterial lysates; pidotimod; probiotics

2. INTRODUCTION AND PURPOSE

Asthma is a chronic respiratory tract disease with an increasing prevalence. It affects about 300 million people worldwide and remains the most common cause of respiratory morbidity.[1] The increasing prevalence of the disease remains unclear, but it is believed that the phenomenon is probably associated with lifestyle changes and increased urbanization worldwide. Moreover, research shows that asthma may be caused by prenatal risk factors including maternal tobacco smoking, cesarean section, stress, and low socioeconomic status.[2] Furthermore, the disease is closely linked with other immune-mediated disorders such as allergic rhinitis, conjunctivitis, and atopic dermatitis.[3]

The most common symptoms reported by patients are wheezing, chest tightness, and shortness of breath.[4] The manifestations affect patients' quality of life by sleep disturbance and lead to an increased rate of anxiety, depression, and alexithymia among patients.[5]
Described manifestations and a significant impact on patients' life, make it necessary to conduct effective treatment. Guidelines classify asthma treatment into 4 or 5 steps by the severity of symptoms and extent of disease control. Every step has its own combination of controller drugs. The most used are inhaled ICSs, LABAs, LTRAs and, IgE-specific monoclonal antibody omalizumab.[6] However, medications are burdened with side effects and their effectiveness is limited, thus there is an urgent need to find new therapy approaches.
The research concerning the use of nonspecific immunomodulatory compounds in atopic diseases has been gathering pace in recent years. Especially probiotics, bacterial lysates (BLs), and pidotimod have shown that they can affect asthma course.[7-12]

In this review, our goal is to summarize the results, present challenges, and describe new ideas for the use of nonspecific immunomodulatory compounds in asthma treatment. The analysis of the previously published studies was conducted by searching the PubMed and Scopus databases, focusing on the last 15 years of publication.

3. DESCRIPTION OF THE STATE OF KNOWLEDGE

3.1. PROBIOTICS

The underlying mechanism of action of probiotics in allergic diseases remains unclear however, some studies show that they might modulate the intestinal microbiota and regulate the inflammatory response. Bearing in mind that atopic disorders, as asthma, are characterized by Th2 response polarization, it is eligible to conduct treatment that reverse unstable Th1/Th2 balance. According to studies, immunomodulatory compounds, like probiotics, can modify the immunologic response by elevating levels of IFN-gamma, which is Th1 response cytokine, and decreasing IL-4 (Th2 specific cytokine). In recent years some meta-analyses concerning the use of probiotics in asthma treatment were conducted.

In 2015 Zuccotti and al. presented a meta-analysis which aim was to evaluate the effect of probiotic supplementation during pregnancy or early infancy for preventing atopic disorders. Seventeen studies with a total of 4755 children were included. Eight studies were concerned about asthma and wheezing. There was no significant difference in terms of prevention of asthma (RR 0.99 [95% CI: 0.77–1.27], P = 0.95). Moreover, the data concerning benefits of probiotics use in wheezing showed similar results (RR 1.02 [95% CI: 0.89–1.17], P = 0.76; fixed-effect analysis).[8] The outcome of the meta-analysis consists of the literature. A large meta-analysis by Elazab et al. showed that prenatal and/or early infant probiotic administration reduces the risk of atopic sensitization but may not reduce the risk of asthma or wheezing.[13] Moreover, Tang et al. found that there is no sufficient evidence to recommend probiotics during pregnancy or early infancy in order to prevent asthma in children.[14]

In 2018 Lin et al. presented the meta-analysis showing the benefits of probiotics supplementation in children with asthma. Eleven studies with a total of 910 children were enrolled in the analysis. The data revealed that children receiving probiotics had fewer episodes of asthma than the placebo group (RR 1.3, 95% CI 1.06–1.59). Moreover, the reduction of IL-4 (mean differences −2.34, 95% CI −3.38, −1.29) and increased IFN-gamma levels (mean differences 2.5, 95% CI 1.23–3.76) were also observed. Nevertheless, there was no statistically significant difference in childhood asthma control test, asthmatic symptoms

night and day, the number of symptom-free days, forced expiratory volume, and peak expiratory flow. The authors of the analysis admit that unsatisfactory results may be caused by low sample studies that were enrolled.[7]

Currently, no guidelines are accepting the use of probiotics in asthma treatment. The GINA report refers to the negative results of meta-analyses.[6] To sum up, there is an urgent need to conduct more large sample studies concerning the use of probiotics, which may be a new way in asthma therapy.

3.2 BACTERIAL LYSATES

Bacterial lysates consist of inactivated bacterial extracts from the most common pathogens of the respiratory tract. They are divided into two groups based on the methods used to produce the mixture: PMBL (Polyvalent Mechanical Bacterial Lysate) and PCBL (Polyvalent Chemical Bacterial Lysate). The underlying mechanism of action of BLs is not completely clear, but the research suggests that they promote immune response by reversing Th1/Th2 balance which results in reducing the likelihood of allergen-induced airway hyperresponsiveness during asthma exacerbations.[15] Moreover, the treatment reduces the frequency of viral infections (triggering factor) by activating macrophages, releasing antiviral cytokines, and neutrophil recruitment.[16]

In 2018 Yin et al. published a meta-analysis concerning the use of the most popular PCBL-OM-85 in recurrent respiratory tract infections. Fifty-three studies involving 4851 pediatric patients were included in the analysis. Eight of them (702 patients) showed the effect of 0M-85 in a reduction of wheezing episodes. The therapy resulted in a decrease of wheezing duration (mean difference – 3.37; 95% CI: – 4.25, – 2.22). Moreover, there were not many several side effects of the treatment. Mild gastrointestinal symptoms and rash were the most common and they did not interfere with the treatment (RR = 1.39; 95% CI: 1.02, 1.88, P = 0.04).[9]

In 2020 the meta-analysis concerning the beneficial effect of PMBL and PCBL treatment in the prevention of wheezing episodes and asthma exacerbations was conducted by de Boer et al. Five studies were included in the meta-analysis. Research showed that BLs therapy caused a decrease of both wheezing episodes (mean difference -2.35 (-3.03- -1.67), $p<0.001$) and asthma exacerbations in children (mean difference -0.90 (-1.23- -0.57), $p<0.001$). Moreover, the treatment resulted in the reduction of antibiotic use and the decrease in wheezing episodes duration. No significant adverse effects were recorded. [10]

Currently, in GINA guidelines there is no mention of BLs use in asthma treatment. However, researchers suggest that BLs have a high potential and need further research.[6]

3.3 PIDOTIMOD

Pidotimod is a synthetic dipeptide that affects both innate and adaptive immunity. It stimulates two PRRs, Toll-like receptor 2 and Toll-like receptor 4. It is well known that nucleotide polymorphisms of PRRs which result in reduced expression of them correlate with the severity of atopic disorders. [17] Pidotimod by stimulating PRRs increase the release of antimicrobial peptides and improved mucociliary transport.[18] In recent years two studies concerning the use of pidotimod in respiratory tract infections (RTIs) and related condition obstructive syndrome (OS) were conducted.[11, 12] Actually, there are no high-quality analyzes on the efficacy of pidotimod in asthma, although RTIs and OS are connected with the disease.

In 2011 Lokshina et al. conducted the study which aim was to evaluate the clinical efficacy and safety of pidotimod treatment in children with acute respiratory infections and obstructive syndrome. Sixty patients were enrolled (30 to pidotimod treatment group, and 30 to control group). Children in the first group were treated with pidotimod two times daily for 14 days, and patients in the control group received standard treatment. The clinical course of the disease was controlled twelve months following the end of treatment. Research showed that pidotimod induced a statistically significant decrease in cytokines (IL-2, IL-8, IFN-gamma) and an increase of sIgA (secretory IgA). Moreover, the number of RTIs was lower in the pidotimod treated group, and episodes of respiratory tract obstructions occurred rarely.[12]

Three years later, Namazova-Baranova et al. conducted a similar study concerning the use of pidotimod in children with RTIs. Patients were assigned to the pidotimod treated and placebo groups. After 30-days of therapy children were followed up for 6 months. The number of RTIs was measured in three time points. The research showed that the therapy course led to the improvement in the rate of RTIs recurrence within 3 months. Moreover, quick elimination of symptoms and a faster recovery were observed. Furthermore, maintaining the levels of IL-8 confirmed the immunomodulatory effect of pidotimod.[11]

To sum up, no studies are assessing the impact of pidotimod on the rate of asthma exacerbations. However, as described before, the treatment reduced the number of RTIs, which are tightly connected with asthma attacks, thus there is a great hope that this product will improve asthma course. Currently, there is no mention of pidotimod in GINA guidelines.[6]

4. CONCLUSIONS

Although the research has been gathering pace in recent years, the data concerning the use of immunomodulatory compounds in asthma treatment remains limited. However, described studies enable us to draw some conclusions. Firstly, probiotics and pidotimod seem to be inefficient in asthma prevention, although they can be used to reduce the number of wheezing and RTIs, which are linked to asthma. Pidotimod seems to have high clinical and immunological effects in the treatment of children with RTIs, however, this result must be viewed through a prism of skepticism due to the low quality of the studies. Bacterial lysates pretend to be the most effective among described preparations. Moreover, the data regarding their usage in asthma treatment is the largest, however, there is still a huge need to conduct more, higher-quality trials.

Considering the limited data concerning the use of immunomodulatory preparations in asthma treatment currently, there is no mention of the therapy in GINA guidelines. Moreover, recommendations seem to be ignorant of the recent data. Bearing in mind the improvement that occurs after described treatment and decrease in the number of asthma exacerbations consideration of their usage as complementary therapies must be given more consideration.

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