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Anti-inflammatory effect of macrolides in obstructive pulmonary diseases

Przeciwzapalne działanie antybiotyków makroidalnych w obturacyjnych chorobach płuc

Chlamydia pneumoniae and *Mycoplasma pneumoniae* are important etiological factors in infections of the upper respiratory tract and community-acquired infections, called atypical lung diseases. For many years the hypothesis of the role of infection with these two microorganisms has been considered in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD). This study presents available data on the role of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in the pathogenesis of some obstructive lung diseases in humans. There are also data on anti-inflammatory effect of macrolides, suggesting possible use of this group of antibiotics in the treatment of chronic diseases of the respiratory tract, especially asthma.

Many studies confirm the role of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in exacerbation in COPD [29, 30, 31, 38] and in triggering and modification of the course of asthma in adults and children [16, 17, 18, 20, 29, 36, 37]. Biscione et. al. found the presence of *Chlamydia pneumoniae* (met. PCR) in 37% of children hospitalized for acute bronchial obstruction, most often in the course of asthma [9]. In a similar study Kocabas et al. found serologic features of severe infection with these microorganisms in 27% of asthmatic children, suggesting causative effect between infection with *Chlamydia pneumoniae*, and increase in the severity of asthma [23]. Another group of researchers found that children suffering from asthma with some symptoms of chronic infection with *Chlamydia pneumoniae* experience exacerbation of the disease more often than children without this infection [14]. A special risk group for chronic infection with above mentioned microorganisms are children and adults suffering from asthma who are often treated with oral glucocorticosteroids and patients with severe cases of asthma accompanied by infections of respiratory tract when antibiotics are often overused [19, 28].

Hahn was one of the first researchers who proved relationship between the infection with Chlamydia pneumoniae and obstructive bronchial diseases in adults [18].

Other researchers, among them from Lublin, found out that repeated infections with these microorganisms may be the cause of asthma exacerbation [19, 36], both in atopic and non-atopic patients [5].

A similar role in the pathogenesis of infectious and obstructive diseases of the respiratory tract is attributed to *Mycoplasma pneumoniae*. Infection with this microorganism is often found in children suffering from asthma. Esposito et al. revealed in their very well documented study that symptoms of severe infection with *Mycoplasma pneumoniae* (titre of specific IgM ≥ 1:100 or IgG ≥ 1:400 or PCR+) were seen in 22.5% of children hospitalized for wheeze. These were mostly children over 5 years, and 94% of this group had had episodes of bronchial obstruction [16]. Kraft et al. after examining bronchoalveolar lavage fluid revealed the presence of *Mycoplasma pneumoniae* (using PCR) in almost 90% of adults with chronic asthma [28]. They suggest that this microorganism may be an important cofactor in the pathogenesis of chronic asthma [27]. Other authors confirmed the role of infection with *Mycoplasma pneumoniae* in asthma exacerbation [10, 26], although there were also some conflicting reports [12].

Considering high frequency of infection with atypical bacteria in patients with asthma and their adverse effect on the course of this disease, in the 1990s there was a rebirth of the idea of the use of macrolide antibiotics for the treatment of asthmatic patients. Macrolides have been used for the treatment of asthma for over 40 years [22]. Although clinical experience confirmed the usefulness of administering macrolides in some forms of the disease, the report by Spector et al. from 1974 proved clinical effectiveness of one of the first macrolide (troleandomycin-TAO) in steroid-dependent asthma, although studies were carried out on a very small group of patients [42]. The following reports from 1980s and the beginning of 1990s presented different possible mechanisms that might contribute to the effectiveness of TAO therapy in chronic steroid-dependent asthma [7, 47]. It seemed at that time that, apart from antibacterial effect, TAO decreases clearance of glucocorticosteroids (GKS) administered *per os*, and especially metyloprednisone, that enabled decrease in doses of GKS and reduced adverse side effects [7]. Some researchers revealed also immunosuppressive effect of TAO [49] and recommended this antibiotic for the treatment of severe cases of asthma, even in children [45, 47]. However in the following years several critical reports were published. In one of them Nelson et al. presented many arguments against the effectiveness of TAO therapy, that resulted in excluding this macrolide from recent anti-asthmatic drugs [8, 35] due to its many adverse side effects, and metaanalysis published lately by Evans et al. did not confirm anti-asthmatic effect of this antibiotic [15].

The appearance of new macrolide antibiotics (azithromycin, clarithromycin, roxithromycin, dirithromycin) gave a new stimulus for a detailed study of various properties of this group of antibacterial drugs [6]. Many experimental and clinical studies from the last 10 years revealed other than antibacterial properties of macrolides, that may explain their clinical effectiveness in the treatment of chronic inflammatory diseases of the respiratory tract, and especially in asthma and diffuse bronchiolitis. It has

been demonstrated that this group of antibiotics has anti-inflammatory and anti-oxidative effect [2, 4, 11, 13, 25, 32, 33, 41, 43, 44, 48], and some researchers even mention anti-asthmatic effect [25]. Most important non-antibiotic effects of macrolides are presented in Table 1.

First studies presenting anti-inflammatory and anti-oxidative effects of macrolide antibiotics were carried out by Miyatake [33]. He presented the evidence for the relationship between decrease in non-specific hyperreactivity of bronchi in adults with asthma treated with erythromycin and inhibition of production of reactive oxygenic forms and chemotaxia of neutrophils. Some time later Konno et al. found that the decrease in non-specific bronchial hyperreactivity in patients with asthma may be related to the inhibitory effect of macrolides on the production of interleukines (IL-2, IL-3, IL-4) by lymphocytes T and TNF-alpha (tumour necrosis factor – alpha) by monocytes [25]. Then Nakajima et al. discovered immunosuppressive effect of roxithromycin on macrophages and dendritic cells, that may block the response by IL-2 from lymphocytes obtained from flour dust mites stimulated by antigens in asthmatic children [34]. Thus they revealed a possible inhibitory effect of macrolides on early stages of allergic reaction. Meloni and Adachi in their studies *in vitro* and *in vivo* discovered a possibility of inhibiting the activity of NADPH-oxidase from neutrophils, the decrease in production of IL-8 and TNF-alpha by alveolar macrophages, and also the decrease in the number of neutrophils in bronchoalveolar lavage fluid, inhibition of degranulation of neutrophils by inhibiting mieloperoxidase, neutrophil elastase and N-acetyl-glucosamidase in patients treated with various macrolide antibiotics [2, 32].

In the middle of 1990s some suggestions appeared that the administration of low doses of macrolides for several weeks may be useful in the treatment of asthma [19, 21, 40]. One of the first reports on this subject dealt with children. Shimizu et al. showed a beneficial effect of roxithromycin administered daily in a dose of 150 mg for 8 weeks for non-specific bronchi hyperreactivity detected by the use of histamine test in asthmatic children, although the treatment did not affect behaviour of FEV1 (Forced Expiratory Volume in 1 sec.) [40]. Similar results were obtained later by Koh et al. in children with bronchiectasia, where the bronchi hyperreactivity was assessed using the metacholine test [24]. Further explanation of the beneficial effect of macrolides on the course of asthma was found in a very interesting report by Adachi et al. [2]. On the basis of this report it may be concluded that macrolides shorten the survival time of eosinophils by inducing their apoptosis. It may be of importance in limiting eosinophilic inflammation of bronchial mucous membrane in asthmatic patients treated with macrolide antibiotics.

Other researchers presented the evidence for a stabilizing effect of macrolides on cellular membranes of neutrophiles, that may have also a beneficial effect in asthma [4].

Reports from the last 5 years revealed other possible mechanisms of anti-inflammatory effect of macrolide antibiotics. Takizawa et al. proved the inhibitory effect of macrolides on the expression of endoteline-1 on human bronchial epithelial cells and this fact may explain clinical effectiveness of this group of antibiotics in asthmatic

patients [44]. A positive effect following 8-week roxithromycin treatment of aspirin-induced asthma was also demonstrated. This resulted in clinical improvement, the decrease in eosinophils and the ECP level (eosinophil cation protein) in serum and sputum [41]. A report by Abe et al. presented anti-inflammatory effect of macrolides in a new light. Their study suggested that some macrolides may inhibit the transcription of a gene IL-8 in cells of bronchial epithelium, mainly due to AP-1 molecule (activator protein-1 binding site) [1]. It was also demonstrated that after 6-week treatment with clarithromycin a decrease in the expression of neurokinine-1 and substance P in the respiratory tract of asthmatic patients is observed, the fact that suggests the possibility of inhibiting neurogenic inflammation [11]. It is also suggested that azithromycin may have a protective effect against the ozone-induced inflammation of the respiratory tract [13].

The above reports became the scientific basis for first attempts to use macrolide antibiotics in the asthma treatment. Hahn was one of the first researchers who demonstrated clinical and spirometric improvement in adults with chronic moderate or severe asthma due to *Chlamydia pneumoniae* following 4-week treatment with macrolides (azithromycin or erythromycin) [19]. Then other researchers demonstrated the effectiveness of many weeks lasting therapy with various macrolides in different clinical forms of asthma in adults [10, 21, 26, 27, 33, 41] and in children [16, 40]. In one of recently published and well documented report by Amayasu et al. it was demonstrated that following 8-week treatment with macrolide antibiotic in patients suffering from asthma there was a decrease in eosinophilia in serum and sputum, and in ECP level in sputum, and also a decrease in non-specific bronchial hyperreactivity assessed by metacholine test [3]. This report confirmed antibacterial effect of macrolide antibiotics in the inhibition of eosinophilic inflammation of bronchial mucous membrane in patients with asthma, previously found in *in vitro* studies. Esposito et al. demonstrated that children with exacerbated asthma and symptoms of acute infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* treated with macrolides had much fewer episodes of wheezing for the next 3 months of observation in comparison with the group not treated with this antibiotic [16].

For the treatment of inflammatory diseases of the respiratory tract (including asthma), other properties of macrolides are also important: they reduce mucus production [46], and improve its physical properties that help in its evacuation from the respiratory tract [39]. Presented above and probably other still unknown non-antibiotic properties of macrolides may suggest their use in the treatment of chronic inflammatory diseases of the respiratory tract, such as asthma, COPD, chronic bronchitis, bronchiectasia, diffused bronchiolitis and cystic fibrosis. Immuno-modulatory properties of this group of antibiotics, studied so far, may encourage the continuation of research in this field.

Table 1. Anti-inflammatory, anti-oxidative and anti-asthmatic properties of macrolide antibiotics

Therapeutic effects	Macrolide antibiotic	Author, year, ref. no.
Inhibition of IL-2, IL-3 and IL-4 production by lymphocytes T and of TNF-alpha by monocytes	Roxithromycin	Konno 1994 [25]
Inducing apoptosis of eosinophils	Erythromycin Clarithromycin	Adachi 1996 [2]
Stabilisation of mucous membrane in neutrophiles Erythromycin	Azithromycin	Anderson 1996 [4]
Inhibition of the activity of NADPH oxydase and elastase of neutrophiles, decrease in neutrophil in BAL-u, inhibition of degranulation of neutrophils	Erythromycin Flurithromycin	Meloni 1997 [32]
Normalisation of indicators of the oxidative – anti-oxidative system	Azithromycin Erythromycin	Yashina 1997 [48]
Reduced production of IL-8 and TNF-alpha in alveolar macrophages	Clarithromycin Erythromycin	Sugiyama 1997 [43]
Inhibition of endotheline-1 expression	Clarithromycin	Takizawa 1998 [44]
Inhibition of neurogenic inflammation	Clarithromycin	Chu 1998 [11]
Decrease in eosinophilia and concentration of eosinophil cation protein in serum and sputum in patients with bronchial asthma	Roxithromycin	Shoji 1999 [41]
Partial blockage of response from respiratory tract (FEV1, FVC, metacholine test, clinical symptoms) following O3 provocation	Azithromycin	Criqui 2000 [13]

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STRESZCZENIE

Chlamydia pneumoniae and *Mycoplasma pneumoniae* są ważnymi czynnikami etiologicznymi zakażeń górnych dróg oddechowych oraz pozaszpitalnych, tzw. atypowych zapaleń płuc. Patogeny te biorą również udział w patogenezie astmy oraz przewlekłej obturacyjnej choroby płuc. Istnieje wiele danych o przeciwzapalnych właściwościach makrolidów, sugerujących ewentualne wykorzystanie tej grupy antybiotyków w terapii przewlekłych schorzeń układu oddechowego, a szczególnie rozsianego zapalenia oskrzelików i astmy oskrzelowej.