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AZITHROMYCIN IN TREATMENT OF PATIENTS WITH ASTHMA AND *C. PNEUMONIAE* INFECTION

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Abstract

Chronic *C. pneumoniae* infection has been suggested as a cause for adult onset of asthma. There are data to suggest that infectious organisms, particularly the atypical bacteria *C. pneumoniae*, may be involved in asthma pathogenesis. The significance of these organisms is as yet unclear. It is not known whether this organism was allowed to persist after an infection, or was present prior to the development of asthma. The purpose of this study was to determine whether anti-chlamydial treatment with azithromycin will improve asthma symptoms and lung function in asthmatic patients positive for *C. pneumoniae*.

For this purpose, 20 patients (mean age 39.8 years) with mild asthma were treated a median of 8 weeks with azithromycin 1000 mg once weekly. All patients had *C. pneumoniae* infection detected by Seeplex Multiplex PCR in sputum and positive IgG titre > 1 : 64 and IgA titre > 1 : 16 antibodies against *C. pneumoniae*. Post treatment lung function, symptom score (cough, wheezing, dyspnea), morning and evening PEF values and β2-agonist use were compared with baseline values.

After 8 weeks of treatment with azithromycin there was a significant reduction in symptom score ($p < 0.001$) and a significant improvement in lung function FEV_1 ($p < 0.001$), morning and evening PEF values $p < 0.05$ Wilcoxon matched Pairs test. We also found a reduction in β2-agonist use, but it was not statistically significant.

Treatment with azithromycin significantly improved asthma symptoms and lung function, indicating that *C. pneumoniae* may play an important role in enhancing the inflammatory processes in the lower airways.

Key words: asthma, *C. pneumoniae*, azithromycin.

Introduction

C. pneumoniae is an intracellular pathogen and a common cause of respiratory tract infections including sinusitis, bronchitis and pneumonia [1]. Much evidence indicates that the *C. pneumoniae* infection itself is related to a great number of chronic diseases. So far, the relation between atherosclerosis and *C. pneumoniae* infection has been documented [2], and *C. pneumoniae* infection also can have an effect on asthma manifestation [3–7].

In literature, there is a lot of data which suggest that infections with atypical bacteria such as *C. pneumoniae* may play an important role in asthma pathogenesis [8]. Also, there is data in favour of the possible implication of *C. pneumoniae* in asthma exacerbation [9].

C. pneumoniae infections are characterrized with immunopathological damage to the host tissue, including the lungs. Infections caused by this microorganism are associated with acute bronchitis occurrence [10], bronchial hyperac-

tivity [11], asthmatic attack [12] and asthma severity [11].

The serological evidence of *C. pneumoniae* infection is not associated with an increase in mild asthma prevalence in children and young adults.

But there is evidence that *C. pneumoniae* infection may have an effect on asthma immensity. The relation between high titres of immunoglobulin G and A (IgG and IgA) antibodies against *C. pneumoniae* and asthma severity is well described [5].

C. pneumoniae infection leads to increased formation of pro-inflammatory cytokines including interleukin-1 (IL-1), tumour necrosis factor-alpha (TNF-α), granulocyte-macrophage colony stimulating factor (GM-CSF) and RANTES. These findings give an explanation of the question as to how chronic infection with *C. pneumoniae* leads to increased asthma severity.

C. pneumoniae is detected with PCR in the upper and lower airways in some patients with mild and moderate asthma. The importance of these findings regarding the asthmatic patients remains unclear. It is not known whether *C. pneumoniae* persist in the airways after the infection or are present in the airways before the asthma development. The observation that *C. pneumoniae* is present in the airways before asthma development is quite interesting. There is data that patients with acute *C. pneumoniae* infection develop asthma and that there is a considerable improvement of the lung function and asthma symptoms after antibiotic therapy against *C. pneumoniae* [13].

If the *C. pneumoniae* infection affects asthma severity, then the antibiotic treatment directed against *C. pneumoniae* should lead to asthma improvement and control.

In a study carried out by Hahn, et al. 46 adult *C. pneumoniae* seropositive patients with stabile persistent asthma were treated 3–9 weeks with antibiotics (mostly azithromycin). More than half of the examined patients had considerable improvement of their symptoms or had complete asthma resolution [14].

We carried out a study in which we evaluated the effects of azithromycin in a single-dose of 1000 mg a week over 8 weeks, in patients with mild asthma and *C. pneumoniae* infection, diagnosed on the basis of the increase of IgG or IgA antibodies titre against *C. pneumoniae* and positive PCR for *C. pneumoniae* in sputum.

Methods

In our study, we examined 20 patients (11 women and 9 men), from 18 to 60 years of age, mean of 39.8 years, with asthma diagnosed by a physician, FEV1 ≥ 60% of the predicted values, or increased values of FEV1 ≥ 15% after salbutamol inhalation, or with REF variations (diurnal) ≥ 15% in a period of 7 to 14 days.

As including criteria for the study the examinees were supposed to have increased IgG titre of antibodies for *C. pneumoniae* ≥ 1 : 64 and/or IgA titre ≥ 1 : 16 and a total symptom score ≥ 3 (chart 1), in a period of 7 days from a total of 14 days during the run-in period.

Chart 1

Asthma Symptom Score

Symptom intensity	
0	No symptoms
1	Mild symptoms
2	Moderate symptoms
3	Severe symptoms
Evaluated Symptoms	
	Cough
	Laboured breathing (dyspnea)
	Chest Wheezing
	Asphyxia during sleep
	Maximum possible points = 12

The examinees did not fulfill the inclusive criteria if they were on macrolides, quinolones or tetracyclines for 4 weeks before participating in the study or had been on therapy with any of the aforementioned medicines for longer than 2 weeks in the last 4 months. Other medicines which were not allowed were terfenadine or astemizole. Also, an excluding criteria was 20 years smoking history (one pack per day over 20 years), bronchiectasis, any kind of serious systematic illnesses, macrolide hypersensitivity or any kind of significant change of asthma treatment in the past month (including the use of oral corticosteroids in the last month). Any kind of asthma treatment was allowed unless there were changes in the dosage (dosage increase). Use of oral corticosteroids in the last month before the start of treatment was also an exclusive criterion. Also, respiratory tract

infection (followed by intensive cough and voluminous/ purulent sputum) during the inclusion (run-in) period was an excluding criterion, or if they had impaired hepatic function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin above the normal values) or serum creatinine > 150 micromole/L.

The study consisted of a 2-week inclusion (run-in) period, and an 8-week therapy period. From the sputum of each patient a PCR for *C. pneumoniae* was performed with Seeplex Multiplex PCR (Seegene Inc., Korea) performed at University Medicine, Southampton General Hospital, UK. Patients with positive findings were allowed to be included in the study if they fulfilled other inclusion criteria. Serological analyses for *C. pneumoniae* were carried out for every examinee during a screening visit. Antibodies against *C. pneumoniae* were measured with method of micro immunofluorescence (LabSystems, Helsinki, Finland). Subjects who had IgG titre for *C. pneumoniae* of 1 : 64 or IgA titre of 1 : 16 fulfilled the criteria for participating in the study and passed the inclusion (run-in) period. In the inclusion (run-in) period, FEV1, FVC and bronchodilator reversibility were monitored. Immediately after measurements, the examinees were given a mini peak flow meter Vitalograph, and a diary. PEF measurement and symptom score diaries were recorded by the patients twice a day over two weeks (Chart 1). Three measurements of PEF were carried out in the morning after awakening, and in the evening before bedtime, before taking therapy, and so the best of three measurements was noted in the diary. Subjects who fulfilled the criteria for participation in the study were treated with 1000 mg azithromycin once a week for 8 weeks. The examinees did PEF every day, and got their usual anti-asthmatic therapy unaltered in the last month. Patients could use a bronchodilator if necessary as rescue medication.

Spirometry and PEF measurements were carried out at the beginning and at the end of the study. Compliancy was assessed using PEF measurement records, questionnaires and a recount of tablets received back.

Primary objects were:
- FEV1 changes
- Symptom score (symptom score) changes

Secondary objects were:
- Morning PEF changes
- Evening PEF changes
- Changes in inhale β2-agonist usage.

Statistical analysis

In order to define whether there was a significant parameter difference before and after the therapy, the Wilicoxon matched Pairs test was used. The difference between results where p values were less than 0.05 ($p < 0.05$) was considered significant.

Results

From a total of 54 screened subjects, 30 were PCR positive for *C. pneumoniae*, and 20 fulfilled all the inclusive criteria and agreed to participate in the study.

C. pneumoniae titre distribution for the analysis needs is shown in chart 2.

Chart 2

Starting (basic) characteristics

	Azithromycin
Number of examinees	20
Average Age (SD)	39.8
M/F	9/11
Inhale steroids usage, %	80.4%
IgG antibodies against *C. pneumoniae*	109.2
Geometric mean titre (95% CI)	(89.0–130.3)
C. pneumoniae IgA antibodies	11.5
Geometric mean titre (95% CI)	(10.2–13.9)
Abbreviations: IgG – Immunoglobulin-G, IgA – Immunoglobulin-A	

All parameters measured in the study before and after 8 weeks treatment with azithromycin are shown in chart 3.

Chart 3

Starting (basic) characteristics

	Before therapy	After therapy
Average FEV1, L (SD)	2.48 ± 0.34	2.62 ± 0.29
Average PEF:		
Morning, L/min (SD)	369.1 ± 44	390.2 ± 48
Evening, L/min (SD)	382.5 ± 47	402.3 ± 50
Daily symptom score (SD)	5.1 ± 0.60	4.73 ± 0.79
β2 agonists usage		
Average number of inhalations during the day (SD)	2.4 ± 1.6	1.8 ± 2.3
Average number of inhalations during the night (SD)	1.2 ± 1.5	0.8 ± 1.9

FEV1

The azithromycin therapy effect on FEV1 is shown in Figure 1.

After the azithromycin treatment there was a significant improvement in the FEV1 values from mean 2.48 L/min to mean 2.62 L/min ($p < 0.001$).

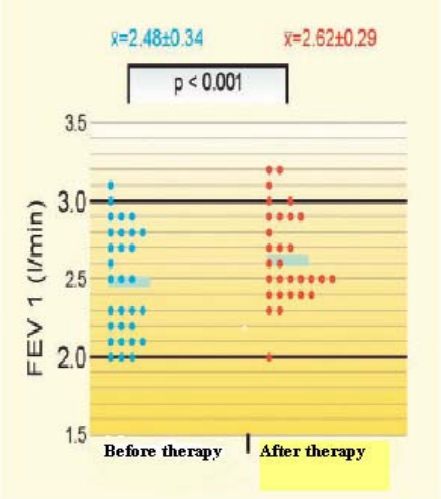

Figure 1 – Effects of azithromycin on FEV1 in patients with asthma

Symptom score

The results of the daily total symptoms noted by the patients in their diaries 2 weeks before the start of therapy and 2 weeks after the finish of therapy are shown in Figure 2.

At the end of the study, the daily total symptom score reduced significantly from mean 5.1 to mean 4.73 ($p < 0.001$).

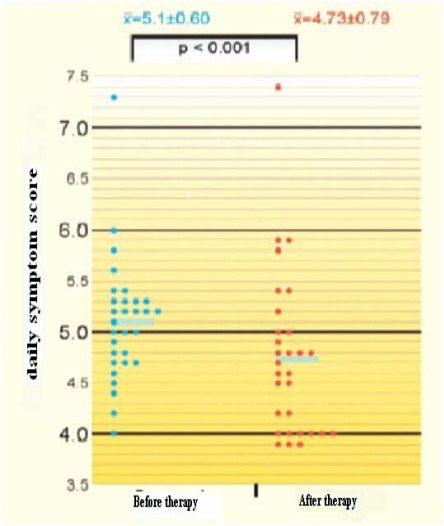

Figure 2 – Effects of azithromycin on daily symptom score in patients with asthma

Peak Expiratory Flow

The therapy effect on morning PEF measures is shown in Figure 3. From the beginning to the end of the 8th week the increase of morning PEF of mean 21.1 L/min from baseline, ($p < 0.05$) was evident.

The azithromycin therapy effect on evening PEF values is shown in Figure 3 (traingles). After the 8-week treatment there came about a significant increase of evening PEF of mean 19.8 L/min from baseline ($p < 0.05$).

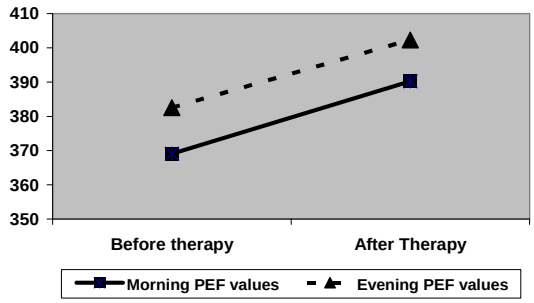

Figure 3 – Morning PEF measurements before and after azithromycin therapy (squares). Morning PEF increase is significantly greater at end of treatment ($p < 0.05$). Evening PEF measurements before and after azithromycin therapy (triangles). Evening PEF increase is significantly greater at end of treatment ($p < 0.05$)

β2-agonist inhalation usage

After the end of azithromycin treatment, there was a decrease in patients' β2 agonist use during the day from an average 2.4 to 1.8 inhalations and during the night from 1.2 to 0.8 inhalations, which in both cases was not statistically significant.

Unwanted effects/(Side effects)

During the 8-week azithromycin treatment there were a total of 4 side effects, one of which was associated with diarrhea, two with nausea and one with headache. There was no crossing the lines of normality in the transaminases and bilirubin in any of the patients.

Discussion

In this study we showed that 8 weeks treatment with azithromycin leads to significant FEV1 ($p < 0.001$) improvement, as well as total symptom-score improvement ($p < 0.001$).

In our study we came to conclusive evidence that the azithromycin treatment leads to persistent improvement of all asthma symp-

toms registered through a total symptom score. Our results are in accordance with those of Hahn, et al. [15] who in 2005 carried out a study on patients with stabile persistent asthma and treated them with azithromycin for 5 weeks. All changes in asthma symptoms, measured on a scale of five points, strongly correlated with the reduced usage of bronchodilator therapy. The evident effect of asthma improvement generally reached its maximum at the end of the study and endured until the last visit, 3 months after the treatment's termination. This result is in accordance with the previously documented open study in which the use of azithromycin on patients had its greatest effect in the third month of the study [9].

However, these results should be warily interpreted because they come from a pilot study in which the principal asthma outcome was not rendered concrete. Yet these preliminary results give a basis for further studies with a greater representtative number of asthma patients and followed for an extended period of time.

In our study, after 8 weeks of azithromycin treatment, the patients had significantly better FEV1 values in comparison to the start of the therapy. Similar results are published by Kraft, et al. [16]. In his study he found significantly increased FEV1 average values. The average FEV1 value before treatment was 67.8% of that predicted and increased by 12.5% after the treatment ($p = 0.003$ in comparison to baseline values). In this study, as well as in ours, there was no placebo group, and the examinees were given a wider spectrum of medicine in various dosages.

But, at the same time, azithromycin is an anti-inflammatory drug. It has been published that macrolides show anti-inflammatory characteristics against neutrophils and lymphocytes [17]. Amasayu, et al. [18] have shown that in patients with mild to moderate asthma who were on 8 weeks treatment with 1000 mg Clarithromycin twice a day, there was an improvement in asthma symptoms and reduction of sputum eosinophils as well as serum eosinophils (eosinophil cationic protein). Also, there was a modest improvement in bronchial hyperactivity. Konno, et al. [19] showed that macrolides reduce TNF-α, IL-3, IL-4 and IL-5 expression in the lungs of mouse models. Also, it has been confirmed that macrolides reduce mucus production and bronchial hyperactivity in vitro [20].

In our study we registered a significant increase in morning and evening PEF. The clinical significance of the alteration of morning and evening PEF values ($p < 0.05$) can be discussed. Our results are in accordance with other studies, where patients with uncontrolled asthma who were on inhaled corticosteroids had increased inhale corticosteroid therapy or were given additional therapy. Fabbri et al. compared the effects of Fluticasone propionate 1.5 mg/daily with Beclamethasone dipropionate 1.5 mg/daily in patients with moderate to severe asthma [21]. Fluticasone propionate is twice as potent as Beclomethasone dipropiate, but morning PEF-increase with Fluticasone propionate was only 15L/min greater than that achieved with Beclomethasone dipropionate. Laviolette, et al. studied the effect of adding Montelukast 10 mg/ daily to uncontrolled asthma patients who were receiving Becalomethasone 200 microgram twice per day [22]. Adding Montelukast led to an improvement of morning PEF values for 10L/min.

There are many potential explanations for the perceived benefit of azithromycin treatment. The anti-inflammatory effect is documented *in vitro* for azithromycin and other macrolide antibiotics [23]. Macrolide drug roxithromicin inhibits the effect of neutrophil oxidase [24, 25] and reduces the production of cytokines, including: IL-6, IL-8 and GM-CSF [16] from epithelial cells of airways as well as IL-5 from splenocytes [27]. In animal models, the macrolides inhibit oedema in mise as a response to karagenine [28] or polyarginine [29]. If azithromycin treatment is beneficial for asthma treatment because of its anti-inflammatory effect, then it would be effective on all groups of asthma patients, regardless of whether they have *C. pneumoniae* infection or not. In this sense all previous studies which used macrolides in asthma treatment are of interest.

Kraft et al. examined 39 asthma subjects in a random study in which patients were treated with Clarithromycin or a placebo, for 6 weeks [30]. Bronchial biopsy and bronchial

alveolar lavage were carried out before the treatment began. The subjects who were PCR positive for *C. pneumoniae* or *Mycoplasma pneumoniae* showed a significant FEV1 improvement as a response to the clarithromycin therapy in contrast to the examinees who were PCR negative. These studies showed that the benefit of macrolide antibiotics against asthma is not only for its anti-inflammatory characteristics.

The greatest problem, however, is the difficulty of eradicating one intracellular pathogen such as *C. pneumoniae* is with just one antibiotic.

Thus, the result of the therapy depends on *C. pneumoniae* eradication. Indeed, if *C. pneumoniae* is to be successfully eradicated, maybe it is necessary for it to be treated with two or more active antibiotics aimed against *C. pneumoniae*, and for the treatment to last longer.

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Резиме

AZITHROMYCIN ВО ЛЕКУВАЊЕТО НА ПАЦИЕНТИ СО АСТМА И ИНФЕКЦИЈА СО *C. PNEUMONIAE*

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Како една од причините за иницирање на астматските напади се смета хроничната инфекција со *C. pneumoniae*. Во литературата се срет-нуваат податоци дека инфективните микроорганизми, особено атипичните бактерии како што е *C. pneumoniae* може да има значајна улога во патогенезата на астмата. Сè уште не е јасна улогата на *C. pneumoniae*. Сè уште не е познато дали овој микроорганизам е присутен во организмот и по инфекцијата со него и дали бил присутен за време на развојот на астмата.

Целта на оваа студија е да одреди дали антихламидијален третман со азитромицин ќе ги подобри симптомите на астмата и белодробната функција кај пациенти со астма особено кои се позитивни на тестовите за *C. pneumoniae*.

За таа цел 20 пациенти на средна возраст од 39.8 години со лесна астма, беа третирани со азитромицин од 1000 мг еднаш неделно во траење од 8 недели. Сите пациенти имаа инфекција со *C. pneumoniae* дијагностицирана преку позитивен Seeplex Multiplex PCR од спутум и позитивен титар на IgG > 1 : 64 и IgA > 1 : 16 антитела против *C. pneumoniae* (ELISA). Притоа ги компариравме резултатите од белодробната функција, целодневните симптоми на астма, PEF вредностите и употребата на β2-агонисти, пред и по терапијата со азитромицин.

По 8-неделен третман со азитромицин, дојде до сигнификантно намалување на целодневните симптоми на астма ($p < 0,001$), сигнификантно подобрување на FEV1 вредностите ($p < 0,001$) и на утринските и вечерни PEF вредности ($p < 0,05$). Исто така регистриравме и намалување на употребата на β2-агонисти но ова намалување не беше сигнификантно.

Третманот со азитромицин сигнификантно ги подобрува асматските симптоми и белодробната функција укажувајќи на можноста дека *C. pneumoniae* можеби има важна улога во зголемувањето на инфламаторните процеси во долните дишни патишта.

Клучни зборови: астма, *C. pneumoniae*, азитромицин.