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Acta Clin Croat 2015; 54:149-158 Original Scientific Paper

SAFETY AND EFFECTIVENESS OF AZITHROMYCIN IN THE TREATMENT OF LOWER RESPIRATORY INFECTIONS: AN INTERNATIONAL, MULTICENTER, NON-COMPARATIVE STUDY

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SUMMARY – The aim of this study was to describe clinical effectiveness of azithromycin in the management of lower respiratory tract infections in daily clinical practice, to examine duration of symptoms after therapy initiation, and to record any possible adverse effects of azithromycin treatment. A total of 153 patients were included in the analysis of the effectiveness of azithromycin: 94 patients with community acquired pneumonia (CAP) and 59 with acute exacerbation of chronic bronchitis (AECB). Clinical effectiveness was assessed as improvement, cure or failure after three-day treatment with azithromycin. The assessment was based on a calculation of clinical score for each diagnosis before treatment and on days 4, 10 and 28 after treatment initiation. Clinical effectiveness of azithromycin was 93.6% in CAP group and 94.9% in AECB group. Azithromycin led to relief of symptoms within three days in 88.6% of CAP patients and 77.2% of AECB patients. Overall, 15 adverse events were reported in 14 (9.1%) patients. The most common adverse events were abdominal pain, diarrhea and vomiting, each reported in four (2.6%) patients. Accordingly, azithromycin was found to have high clinical effectiveness and a small number of adverse events in the treatment of lower respiratory tract infections. ISRCTN38391551.

Key words: *Azithromycin – therapeutic use; Treatment outcome; Community-acquired infections – drug therapy; Pneumonia – drug therapy; Bronchitis, chronic – drug therapy*

Introduction

Lower respiratory tract infections (LRTI) such as community acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB) are common diseases associated with significant morbidity and mortality rates[1-7]. A variety of bacterial species are associated with LRTI. The most common causes of CAP are *Streptococcus (S.) pneumoniae*, *Mycoplasma (M.) pneumoniae*, *Chlamydia (C.) pneumoniae*, *Legionella pneumophila*, followed by viruses[1]. Their incidence varies across different studies and regions, with *S. pneumoniae* and *M. pneumoniae* being most common[8-10]. More recently, two etiology trends have been observed in adult populations: patients older than 65 have more frequently pneumonia caused by *S. pneumoniae*, *Haemophilus influenzae* and respiratory viruses, while the population younger than 65 have more often CAP caused by *M. pneumoniae*[3]. *M. pneumoniae* is a very common pathogen in patients treated outpatiently and is also the most common pathogen in children and young adults[10,11]. In case of AECB,

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Received October 30, 2014, accepted April 22, 2015

bacteria are associated with 50%-70% of infection-related AECB episodes, whereby the most common of them are *H. influenzae, Moraxella catarrhalis* and *S. pneumoniae*[12-16]. Some authors suggest that there are 3 classes of pathogens involved in AECB: 1) respiratory viruses (like influenza, parainfluenza and rhinoviruses), which are responsible for 30% of AECB episodes; 2) atypical bacteria (like *C. pneumoniae*), which are implicated in less than 10% of episodes; and 3) aerobic gram-positive and gram-negative bacteria (like *Pseudomonas aeruginosa*) in 40%-60% of episodes[15].

Due to the lack of rapid, reliable and cost-effective tests, the nature of disease and other practical problems in daily clinical practice, microbiology testing is rarely performed in outpatients. Even if testing is performed and the pathogen is identified, the information is available only after a few days or weeks. Therefore, patients with clinical symptoms of CAP and AECB are treated with antimicrobials on an empiric basis in order to avoid the possible complications and deleterious consequences of LRTI.

Azithromycin has proven to be an extremely efficacious antibiotic with expanded and enhanced antibacterial activity, prolonged and high tissue concentration, and low incidence of gastrointestinal side effects compared to similar antibiotics[5,17-22]. It has a short dosing period and low incidence of adverse drug reactions[23-25]. Azithromycin concentrations in sputum, bronchial mucosa and alveolar macrophages are above the minimal inhibitory concentrations (MICs) for many pathogens for 4 days after a single dose administration[24,25]. In addition, its immunomodulatory activity has been recognized to be of increasing importance and might contribute to the overall therapeutic effect of azithromycin[26].

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) recommends azithromycin as monotherapy for the treatment of CAP in previously healthy patients[27], whereas the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends it as an alternative treatment for outpatients[28]. In most of the countries, azithromycin is one of the recommended treatments for mild to moderate AECB (defined as group 1 patients), whereas in some countries it is used as alternative[29]. In clinical trials, azithromycin showed to be either better or equally well tolerated, compared to other antibiotics[5,20-23,30]. In the last twenty years, resistance of bacteria causing respiratory tract infections has increased, but reports on how it affects the results of treatment are scarce and controversial[31].

The present study describes clinical effectiveness of azithromycin therapy in outpatients, both children and adults, with a range of LRTI in the real world setting. Furthermore, it examined the duration of symptoms after therapy initiation and the possible adverse events.

Methods

Study design and patients

This was an international, multicenter, non-comparative study conducted in 23 centers in Croatia, Macedonia and Bosnia and Herzegovina. Outpatients were enrolled by their primary care physicians in the period from June 2008 to November 2009. Last patient finished the study in December 2009. The study protocol was reviewed and approved by Ethics Committees and regulatory authorities in Croatia, Macedonia and Bosnia and Herzegovina. Each patient and/or patient's parent/legal guardian signed an informed consent form before being included in the study. Out of 155 patients with LRTI included in the study, 154 were included in the safety analysis and 153 in the effectiveness analysis.

Patients with clinical signs and symptoms of LRTI were consecutively included in the study according to the inclusion and exclusion criteria listed in Table 1. The inclusion and exclusion criteria reflect patients who are usually treated by primary care physicians in the real world setting. Adult patients were treated with azithromycin 500 mg tablets once a day for three days. Children were treated with azithromycin 10 mg/kg/day oral suspension for three days. If they were above 50 kg of weight, they were given the adult dose.

Study procedures

On initial, baseline visit, complete medical history was taken and clinical examination conducted. Chest x-ray was obligatory for CAP patients, whereas it was optional for AECB patients. Furthermore, hematologic tests and sputum cultures were collected optionally, which is in accordance with the standard clinical practice in the countries involved, as well as with the IDSA/

Table 1. Inclusion and exclusion criteria

Community acquired pneumonia (CAP)	**Acute exacerbation of chronic bronchitis (AECB)**
Inclusion criteria	**Inclusion criteria**
• Male or female outpatients • Acute onset of disease indicated by the presence of fever • Presence of at least 1 of the specific clinical signs and symptoms such as cough, sputum production and chest pain; • X-ray confirmation of CAP • Signed informed consent form (for minors, parent or legal guardian written consent needs to be obtained)	• Male or female outpatients • History of chronic bronchitis characterized by cough and sputum production for more than two consecutive years and for most days in a consecutive three-month period in each year • Presence of at least 2 specific clinical signs and symptoms such as intensification of preexisting dyspnea, increase in sputum volume, and sputum purulence • Signed informed consent form (for minors, parent or legal guardian written consent needs to be obtained)
Exclusion criteria	**Exclusion criteria**
• Hypersensitivity to macrolides • Treatment with any antibiotic within 14 days prior to enrolment • Participation in any clinical study within 4 weeks prior to enrolment • Prior enrolment in this study • Signs of sepsis based on the presence of at least 2 of 3 criteria: tachypnea (>20 breaths/min), tachycardia (>90 beats/min), hypothermia (<36 °C) or hyperthermia (>40 °C) • Patients who need hospitalization and/or parenteral antibiotic therapy for CAP, as indicated by any of the following: respiratory frequency >20/min, hypotension (systolic blood pressure <90 mm Hg), disturbances of consciousness, oliguric/anuric patients, cyanotic patients	• Hypersensitivity to macrolides • Treatment with any antibiotic within 14 days prior to enrolment • Participation in any clinical study within 4 weeks prior to enrolment • Prior enrolment in this study • Signs of sepsis based on the presence of at least 2 of 3 criteria: tachypnea (>20 breaths/min), tachycardia (>90 beats/min), hypothermia (<36 °C) or hyperthermia (>40 °C)

ATS guidelines. Each patient received Patient Diary in which patients or minor patients' parents had to record the time of azithromycin administration over three days, body temperature (twice daily), adverse events, and time when they felt relief of signs and symptoms (one day, two days, three days or more than three days after therapy initiation). Patients were asked to bring completed diaries on the second visit (day 4). Follow up visits were performed on days 4, 10 and 28.

General and specific clinical signs and symptoms were recorded at each visit. Clinical score was calculated for each diagnosis, as presented in Table 2. The sum of all scores gave a total clinical score, which was considered a measure for clinical findings at each visit. The maximum possible score for CAP was 20 at visit 1 and 23 at other visits, whereas the maximum possible score for AECB was 19 at all visits.

Clinical response to therapy was evaluated as cure (complete disappearance of signs and symptoms present at visit 1); improvement (defervescence with substantial reduction in the intensity of signs and symptoms present at visit 1; no need for additional antimicrobial therapy); failure (progression or recurrence of signs and symptoms and introduction of other antimicrobial therapy); or non-evaluable on days 10 (visit 3) and 28 (visit 4).

Table 2. Clinical score – effectiveness assessment

General clinical signs and symptoms				
Fever (daily peak)	0-Absent	1 – (37.1-38 °C)	2- (38.1-39 °C)	3- (>39 °C)
Chills	0-Absent	1-Present		
Headache	0-Absent	1-Present		
Cough	0-Absent	1-Present		
Rhinitis	0-Absent	1-Present		
Vomiting	0-Absent	1-Present		
Diarrhea	0-Absent	1-Present		
Inappetence	0-Absent	1-Present		
Specific clinical signs and symptoms				
Community acquired pneumonia				
Auscultatory findings at visit (V) 1	0-Absent		2-Present	
Auscultatory findings at V2, V3 and V4	0-Absent	1-Present, but regressed	2-No change	3-Deterioration
Sputum production	0-Absent	1-Mucous (clear exudates)	2-Mucopurulent (white exudates)	3-Purulent (thick, brown or green exudates)
Chest pain	0-Absent		2-Present	
Dyspnea	0-Absent	1-On exertion	2-On motion	3-At rest
Acute exacerbation of chronic bronchitis				
Intensification of pre-existing dyspnea	0-Absent		2-Present	
Dyspnea	0-Absent	1-On exertion	2-On motion	3-At rest
Increase in sputum volume	0-Absent		2-Present	
Sputum purulence	0-Absent		2-Present	

Adverse events were recorded at all post-baseline visits. The adverse events reporting period commenced upon the subject's entry in the study, defined as the time when the informed consent was obtained, and ended at the last visit. The severity, seriousness, causal relationship with study drug and outcome of an adverse event were also recorded. All serious adverse events were reported in accordance with the local regulatory requirements.

Statistics

Categorical data were expressed in frequencies and relevant percentage. The significance of differences in frequencies between relevant subgroups was tested with the χ^2-test or Fisher's exact test when appropriate. For continuous variables, we calculated mean values with standard deviations. Differences between subgroups of interest were tested with Wilcoxon rank-sum test. The primary outcome variable included effectiveness and tolerability expressed as the number (percentage) of cured patients and number (percentage) of patients with adverse drug reactions. The secondary outcome variable was regression of symptoms assessed by total clinical score changes. The missing values of longitudinal variables that describe treatment effectiveness (presence or absence of symptoms or accompanying scores) were imputed following the last observation carried forward to avoid the bias of false-positive results and preserve the power of the study. The generalized linear mixed effects model was used to assess factors independently influencing the clinical score regression. Effectiveness analysis was carried

Table 3. Demographic and baseline data: community acquired pneumonia

	Community acquired pneumonia (N=94)
Age (yrs), median (interquartile)	20.9 (0.3-79.9)
Gender, male (%)	59 (62.8%)
Height (cm), median (interquartile)	157.5 (106.0-170.0)
Weight (kg), median (interquartile)	50.0 (15.0-68.0)
Body mass index, median (interquartile)	20.7 (16.0-23.5)
Body temperature (°C), median (interquartile)	37.9 (37.5-38.3)
Heart rate (beats/min), median (interquartile)	85.0 (78.0-95.0)
Respiratory rate (breaths/min), median (interquartile)	18.0 (16.0-19.0)
Systolic blood pressure (mm Hg), median (interquartile)	120.0 (105.0-130.0)
Diastolic blood pressure (mm Hg), median (interquartile)	75.0 (70.0-80.0)
Auscultatory findings, n (%)	88 (93.6%)
Sputum production, n (%)	
Mucous	30 (31.9%)
Mucopurulent	40 (42.6%)
Purulent	7 (7.4%)
Chest pain, n (%)	39 (41.5%)
Dyspnea, n (%)	
On exertion	22 (23.4%)
On motion	18 (19.1%)
At rest	1 (1.1%)
Pattern of infiltrate – x-ray, n (%)	
Alveolar	12 (12.8%)
Interstitial	22 (23.4%)
Mixed (patchy)	39 (41.5%)
Not specified	21 (22.3%)

out on the intention-to-treat population (patients who had taken at least one dose of azithromycin and presented for at least one post-baseline visit). Safety data were analyzed on the safety population (confirmed to have taken at least one azithromycin dose). All analyses were performed using SAS for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 153 patients with LRTI were included in the effectiveness analysis (94 patients with CAP and 59 patients with AECB). Demographic and baseline characteristics are shown in Table 3 and Table 4.

At the end of the study (day 28), azithromycin was efficacious in 93.6% (88/94) of CAP patients and 94.9% (56/59) of AECB patients. In the CAP group, cure was recorded in 85 patients and improvement in three patients at the end of the study. Follow up chest x-ray was performed in 23 CAP patients. Complete regression was reported in 20 patients and partial regression in three patients. In the AECB group, 67.8% (40/59) of patients were cured, while improvement was observed in 27.1% (16/59) of patients at the end of the study (day 28). There were six failures recorded in the CAP group and three in the AECB group (Table 5).

Clinical score based on the intensity of CAP and AECB signs and symptoms was calculated for each patient. In the CAP group, the score at inclusion ranged between 4.0 and 17.0, median 8.0, suggesting mild to moderate intensity of symptoms. A significant drop of clinical score values occurred three days after treatment initiation and the median clinical score was 0.0 at the end of the study. In the AECB group, the median

Table 4. Demographic and baseline data: acute exacerbation of chronic bronchitis

	Acute exacerbation of chronic bronchitis (N=59)
Age (yrs), median (interquartile)	47.1 (2.8-84.3)
Gender, male (%)	28 (47.5%)
Height (cm), median (interquartile)	165.0 (158.0-175.0)
Weight (kg), median (interquartile)	71.0 (60.0-84.0)
Body mass index, median (interquartile)	25.3 (21.3-28.4)
Body temperature (°C), median (interquartile)	37.8 (37.2-38.0)
Heart rate (beats/min), median (interquartile)	80.0 (76.0-85.0)
Respiratory rate (breaths/min), median (interquartile)	18.0 (126.0-19.0)
Systolic blood pressure (mm Hg), median (interquartile)	130.0 (115.0-140.0)
Diastolic blood pressure (mm Hg), median (interquartile)	80.0 (70.0-85.0)
Intensification of preexisting dyspnea, n (%)	45 (76.3%)
Dyspnea, n (%)	
On exertion	11 (18.6%)
On motion	31 (52.5%)
At rest	9 (15.3%)
Increase in sputum volume, n (%)	56 (94.9%)
Sputum purulence, n (%)	44 (74.6%)

clinical score was 11.0 (range from 9.0 to 12.0) at baseline. In 75% of patients, it was above or equal 11.0 at inclusion. A significant drop of clinical score values occurred three days after treatment initiation, as shown in Figure 1. At the end of the study, clinical score ranged from 0.0 to 1.0, median 0.0. The earliest treatment effect was observed as resolution of fever, which occurred within 48 hours of treatment in both groups.

Antibiotics were taken by 48 (51.1%) CAP patients and 51 (86.4%) AECB patients within a year

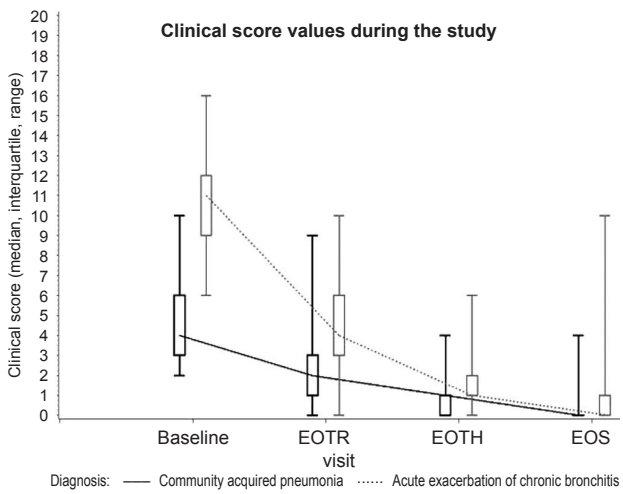

Fig. 1. Clinical score values during the study. Black boxes = community-acquired pneumonia; gray boxes = acute exacerbation of chronic bronchitis; EOTR = end of treatment (day 4); EOTH = end of therapy (day 10); EOS = end of study (day 28)

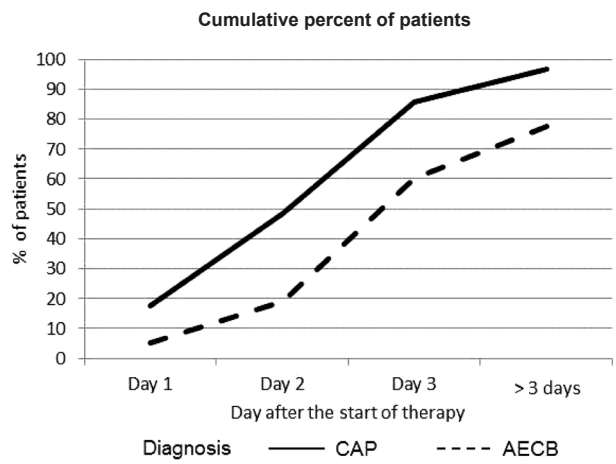

Fig. 2. Cumulative percentage of patients experiencing relief of symptoms during azithromycin treatment. Day = day from therapy initiation; CAP = community acquired pneumonia; AECB = acute exacerbation of chronic bronchitis

before inclusion in the study. Median time of taking antibiotics before inclusion was 2.0 months (25th 75th percentile: 1.0 and 6.0 months) in the CAP group and 3.0 months (25th and 75th percentile: 2.0 and 5.0 months) in the AECB group. Macrolides were taken by 15 (16.0%) CAP patients and 22 (37.3%) AECB patients. Median time of taking any macrolide was 5.5 months (25th and 75th percentile: 2.0 and 6.0 months) in the CAP group and 6.0 months (25th and 75th percentile: 3.0 and 7.0 months) in the AECB group. Previous use of macrolides or other antibiotics did not impact regression of the disease signs and symptoms in CAP patients (p=0.105 and p=0.512, respectively). The impact of previous use of macrolides or other antibiotics in AECB patients could not be assessed due to the low number of patients.

Diaries were received from 91 CAP and 59 AECB patients. Three patients in the CAP group and two in the AECB group did not report their day of relief. Relief of symptoms was observed within three days of therapy initiation in 88.6% (78/88) of CAP patients and 77.2% (44/57) of AECB patients (Table 4), which was in accordance with the drop of clinical score values shown in Figure 1. Figure 2 illustrates cumulative percentage of patients reporting symptom relief from the day of study inclusion. Comorbidities were present in 33.0% (31/94) of CAP patients and 57.6% (34/59) of AECB patients. Hypertension was the most common comorbidity in both groups of patients. Concomitant therapy was reported by 77.0% (53/94) of CAP patients and 84.7% (50/59) of AECB patients. Paracetamol was the most commonly taken drug in the CAP group (15.6% of patients), whereas aminophylline (11.2% of patients) and salbutamol (10.5% of patients) were the most commonly administered drugs in the AECB group.

Table 5. Clinical effectiveness and day of relief as reported by patients

	Community acquired pneumonia (N=94)	Acute exacerbation of chronic bronchitis (N=59)
Clinical effectiveness		
Cure	85 (90.4%)	40 (67.8%)
Improvement	3 (3.2%)	16 (27.1%)
Failure	6 (6.4%)	3 (5.1%)
Cumulative percent of patients with symptom relief upon inclusion		
Day 1	16 (18.2%)	3 (5.3%)
Day 2	28 (31.8%)	11 (19.3%)
Day 3	34 (38.6%)	30 (52.6%)
After >3 days	10 (11.4%)	13 (22.8%)
Clinical score values (median, 25th percentile and 75th percentile)		
Inclusion	8.0 (7.0-11.0)	11.0 (9.0-12.0)
Day 4	4.0 (3.0-5.0)	4.0 (3.0-6.0)
Day 10	1.0 (0.0-2.0)	1.0 (1.0-2.0)
Day 28	0.0 (0.0-0.0)	0.0 (0.0-1.0)

Overall, 15 adverse events were reported in 14 (9.1%) patients. Seven adverse events were characterized as possibly, probably or definitely related to azithromycin. The most common adverse events were abdominal pain, diarrhea and vomiting, each reported in four (2.6%) patients. Therapy was discontinued because of adverse events (nausea and vomiting) in one patient. Two serious adverse events (requiring hospitalization) were reported; however, these events were not related to azithromycin therapy. These two patients were withdrawn from the study; they still received a complete dose of azithromycin.

Discussion

Azithromycin showed high clinical effectiveness in the treatment of CAP and AECB and led to relief of symptoms after three days in the majority of patients participating in this study. Such fast resolution of symptoms can be explained by pharmacokinetic properties of azithromycin and fast achievement of high tissue concentrations[21,23-25], as well as by patient compliance to the three-day treatment regimen of azithromycin. Furthermore, immunomodulatory activity of azithromycin may also contribute to the overall clinical effectiveness shown in this study[26]. High clinical effectiveness observed in this study remained in the ranges of earlier clinical trials conducted more than 20 years ago. However, we must interpret the findings cautiously because these studies were randomized, double blind, comparative, and the etiology was confirmed[5,18,20-23,30]. There also are other factors that might contribute to the

effectiveness of azithromycin, such as mild to moderate incidence of the disease in our patients, and also the possible viral etiology. However, according to the literature, viruses are responsible for significantly less CAP and AECB than bacterial agents[10,29]. Furthermore, in our study, pneumonia was confirmed by x-ray in all patients and about two-thirds of patients had signs and symptoms suggestive of bacterial infection, such as purulent sputum.

Clinical effectiveness of azithromycin was high in the CAP group. This finding is consistent with a systematic review which confirms that azithromycin is the empiric choice for treatment when atypical pneumonia is suspected and is useful for mild and moderate CAP caused by typical pathogens[32]. High clinical effectiveness of azithromycin was also confirmed in the group of patients with AECB, where the majority of patients experienced relief of symptoms after three days of therapy. This is consistent with the results of the observational prospective study by Milestone *et al*., which showed that patients with AECB treated with a 3-day course of azithromycin experienced significant improvements in the health-related quality of life[31].

The majority of patients in the CAP group were younger (mean age 20.1), with a lower number of comorbidities (33.0%) and only a small proportion of patients (16.0%) used macrolides one year before inclusion. On the contrary, the AECB group consisted of older patients (mean age 47.1 years) with more comorbidities (57.6% of patients) who used antibiotics, including macrolides, within one year before inclusion more frequently (86.4% and 37.3%, respectively). Nevertheless, the cure and improvement rates of azithromycin were high in both groups, although the populations differed. We also compared resolution of clinical signs and symptoms in CAP patients based on previous treatment with antibiotics and specifically macrolides, and found that previous antimicrobial therapy had no impact on the resolution of signs and symptoms in CAP patients.

This study was a non-comparative post-marketing observational study lacking confirmed etiology, which might be considered as a limitation of the study. On the other hand, studies of such a design resemble everyday clinical settings and provide insights into the "real-world" effectiveness of a drug. In this study, we demonstrated azithromycin to be efficacious in the treatment of CAP and AECB in a "real-world" setting. Moreover, high clinical effectiveness was confirmed in both patient groups, although they were quite different according to age, comorbidities and previous antimicrobial treatment. The adverse drug reactions reported were in accordance with the acknowledged safety profile of azithromycin. Therefore, we can conclude that azithromycin is a reliable antibiotic treatment for LRTI because of adequate coverage, resulting in fast resolution of symptoms with little adverse drug reactions.

Acknowledgments

The study was sponsored by Pliva Croatia Ltd. We thank the investigators who participated in this study:

Bosnia and Herzegovina: Sarajevo Clinical Hospital Center, University of Sarajevo: Ediba Saračević, Hasan Žutić, Nada Koluder; Tuzla University Clinical Center: Mensur Hadžibeganović

Croatia: Primary care: Biljana Folnović-Tepša, Marina Kraus, Jasminka Nedić, Marina Zubac-Gugić, Nevenka Kaluger, Lovorka Jurić-Bošković, Dubravka Došen, Sanja Čačković, Matilda Tandara, Vjekoslava Amerl-Šakić, Višnja Varović

FYR Macedonia: Department of Pulmonology and Allergology, Skopje: Zlatica Goševa; Institute for Children's Respiratory Diseases, Skopje: Iskra Lazarevska; Primary care: Branka Bilbilovska, Roza Lakinska-Netkova, Violeta Stojanovska, Dragan Mitevski, Elica Stanislevic, Tina Naumoska

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Sažetak

SIGURNOST I DJELOTVORNOST AZITROMICINA U LIJEČENJU INFEKCIJA DONJIH DIŠNIH PUTOVA: MEĐUNARODNA MULTICENTRIČNA NE-USPOREDBENA STUDIJA

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Ciljevi ove studije bili su opisati kliničku djelotvornost azitromicina u liječenju infekcija donjih dišnih putova u kliničkoj praksi, ispitati trajanje simptoma nakon početka terapije te prikupiti podatke o neželjenim događajima. U ispitivanje su bila uključena 153 bolesnika: 94 bolesnika s pneumonijom iz opće populacije te 59 bolesnika s akutnom egzacerbacijom kroničnog bronhitisa. Klinička djelotvornost je ocijenjena kao poboljšanje, izliječenje ili neuspjeh liječenja trodnevnom terapijom azitromicinom. Procjena se osnivala na izračunu kliničkog indeksa za svaku dijagnozu prije početka terapije te nakon 4, 10 i 28 dana. U ovom ispitivanju klinička djelotvornost azitromicina bila je 93,6% u skupini bolesnika s pneumonijom iz opće populacije te 94,9% u bolesnika s akutnom egzacerbacijom kroničnog bronhitisa. Azitromicin je doveo do olakšanja simptoma unutar 3 dana kod 88,6% bolesnika s pneumonijom i 77,2% bolesnika s akutnom egzacerbacijom kroničnog bronhitisa. Zabilježeno je 15 neželjenih događaja kod 14 (9,1%) bolesnika. Najčešći neželjeni događaji su bili dijareja i povraćanje, od kojih je svaki zabilježen u 4 (2,6%) bolesnika. Rezultati ispitivanja pokazuju da azitromicin ima visoku djelotvornost u liječenju infekcija donjih dišnih putova i izaziva mali broj nuspojava. ISRCTN38391551.

Ključne riječi: *Azitromicin – terapijska primjena; Ishod liječenja, procjena; Domicilne infekcije – farmakoterapija; Pneumonija – farmakoterapija; Bronhitis, kronični – farmakoterapija*