TREATMENT OF ACUTE ACQUIRED COMMUNITY PNEUMONIA WITH AZITHROMYCIN

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INTRODUCTION

Community-acquired acute pneumonia still represents a frequent and serious disease with high morbidity, mortality and financial costs, despite multiple and improved antimicrobial therapy schemes or newly appearing ones. Recently changes changes have been observed in regarding epidemiology and treatment of this condition. These consist in an increase in the etiological polymorphism and therapeutic difficulties related to the higher incidence of bacterial strains resistant to antibiotics.

Numerous recent studies have shown an increase in pneumonia incidence in old patients and in those associating another chronic condition (especially those with chronic obstructive lung disease, diabetes, renal failure, cardiac failure, chronic hepatic disorders). On the other hand, new antibiotics have been developed, with a larger antibacterial activity and very
effective in the therapy of community-acquired acute pneumonia.¹

Among the new antibiotics there is azithromycin, a new semisynthetic macrolide, the first representative of a new class of macrolide named azalide. The mechanism of action of azithromycin consists in its binding to sub-unit 50S, thus inhibiting the synthesis of bacterial proteins. Azithromycin is well absorbed after oral administration, passing from serum to tissues and different organs. After administering a single oral dose of 500 mg, bio-availability is 37% and maximal serum concentration of 0.4 mg/l is reached in 2-4 hours.

Therapeutic concentrations of azithromycin are maintained within infected tissues for 5-7 days after the last oral dose. One of the most important characteristics of azithromycin is its uptake by phagocytes, as a transport mechanism to infected tissues where it achieves higher concentrations than in non-infected ones.

Azithromycin reaches high cellular concentrations and demonstrates a very good intracellular activity. The main way of elimination is through bile excretion, mainly as a non-metabolised substance; urinary excretion is responsible for a small fraction. Plasma half-life is approximately 68 hours.

Pharmacokinetic characteristics of azithromycin allow its dosage in a simple therapeutic regimen, associated with a short period of administration, that is a single daily dose for 3 days. Azithromycin has a large range of anti-microbial action including Gram positive germs (Streptococcus pneumoniae, S. pyogenes, S. Viridans, Staphylococcus aureus, etc.), Gram negative (Haemophilus influenzae, H. parainfluenzae, Neisseria gonorrhoea, N. meningitidis, Klebivella spp., etc.), anaerobic (Bacteroides fragilis, Clostridium perfringens, Peptococcus spp, etc.), intracellular microorganisms (Chlamydia pneumoniae, Mycoplasma pneumoniae, Listeria monocytogenes, Legionella pneumophila, etc.)

The purpose of this study is to analyze the clinical and biological efficiency of the treatment with azithromycin compared to amoxicillin and clavulanic acid in hospitalized patients with community-acquired pneumonia.

**MATERIAL AND METHODS**

The study included 45 patients hospitalized in the Infectious Diseases Clinic of Timisoara and subsequently confirmed (clinical, biological and paraclinical) as having community-acquired acute pneumonia.

Patients have been divided into two groups: group A – patients treated with azithromycin and group B - patients treated with amoxicillin and clavulanic acid.

Group A included 23 patients (7 females, 16 males, average age: 39.2±12.3 years) hospitalized in the Infectious Diseases Clinic of Timisoara during 2000 and 2002. Patients have been treated with oral azithromycine (Sunammed-Pliva, 1 tablet=500 mg) 500 mg/day, for a period of 3 days, administered with at least an hour before meal or two hours after meal in order to avoid reduction of drug absorption through interaction with the food consumed.

Group B included 22 patients (10 females, 12 males, average age: 38.3±13.6 years) hospitalized in the Infectious Diseases Clinic of Timisoara during 1999 and 2001. Patients have been treated with amoxycillin and clavulanic acid (Augmentin-BIS, SmithKline-Beecham, 1 tablet contains 875 mg amoxycillin + 125 mg clavulanic acid), 2 tablets/day bid, for a period of 7 days.

The inclusion criteria were: fever of 38°C or more accompanied by repeated chills, sweats, cough with or without expectoration, thoracic pain with or without dyspnea and the presence of the crepitant and subcrepitant rales on a pulmonary area at physical exam of the respiratory system. All patients presented at admission a suggestive radiological image for an area of pulmonary condensation.

This study did not include patients receiving an antibiotic treatment within 7 days prior to hospital admission nor subjects known to have chronic lung disorders (tuberculosis, bronchitis, bronchiectasia, chronic obstructive lung disease, chronic right ventricular insufficiency, lung emphysema). Patients with antecedents of hypersensitivity at common macrolides (including azithromycin) or penicillin were also excluded. Patients with different common hepatic disorders (chronic hepatitis, cirrhosis, etc.) or renal diseases (acute and chronic renal failure, pyelonephritis, glomerulonephritis, etc.) were included.

Patients were followed clinically (fever, cough, expectoration, thoracic pain, dyspnea, crepitant rales, etc.), biologically (leukocytes, ESR, fibrinogen, C reactive protein, sputum cultures) and imagistically (lung X-ray). Clinical criteria have been recorded daily, and biological parameters and radiological control were performed before the initiation of treatment and 8 to 10 days afterwards.

**RESULTS**

Patients were evaluated according to the established clinical, biological and radiological criteria established. Clinical outcome was appreciated as: healing, improvement or failure:

- Healing was considered as complete
disappearance of symptoms and signs of infection without the need to administer a second antibiotic.

- Improvement was defined as partial disappearance of the symptoms and signs of infection without the need to administer a second antibiotic.
- Failure was defined as persistence of symptoms and signs of infection or the necessity to administer a supplementary antibiotic treatment.
- Healing and improvement were considered clinical therapeutic success.

At the end of the treatment phase, 19 patients (86.36%) from the group treated with azithromycin were declared clinically and biologically healed (no fever, no cough, no expectoration, no dyspnea at rest, no vesicular rales and biologic parameters monitored in normal limits); 2 patients (9.09%) presented a partial improvement of symptoms and signs of infection without the need to administer a supplementary antibiotic; treatment failure (4.54%) was noted in a female patient that needed supplementary therapy for 5 days with cefuroxime. (Table 1)

In the group of patients that received Augmentin-BIS (B) 19 subjects (82.60%) have been declared clinically and biologically healed (no fever, no cough, no expectoration, no dyspnea at rest, no vesicular rales and biologic parameters monitored in normal limits); 3 patients (13.04%) presented a partial improvement of symptoms and signs of disease without being necessary to add another antibiotic, and it was reported one case (4.34%) who was given cefuroxime for another 4 days (failure).

Three patients in the group A (13.63%) presented as associated comorbidity essential arterial hypertension, 4 subjects (18.18%) were known with coronary heart disease, 2 patients (9.09%) were recorded with type 2 diabetes, 5 patients (22.72%) presented spasmophilia, 4 subjects (18.18%) had digestive lambliosis, 2 patients (9.09%) were diagnosed with anemic syndrome and one patient (4.34%) was known to have chronic duodenal ulcer.

In the group B, 2 patients (8.69%) had essential arterial hypertension, 3 subjects (13.04%) were recorded with chronic coronary heart disease, one patient (4.34%) was known to have type 2 diabetes mellitus, 2 patients (8.69%) presented spasmophilia, 5 subjects (21.73%) were found with digestive lambliosis and 3 patients (13.04%) have been diagnosed with anemic syndrome.

Clinical evolution confirmed the efficacy of antibiotic treatment in both groups. In group A, fever was remitted after 24 hours in 10 patients (45.45%), after 48 hours in 8 patients (36.36%) and after 36 hours in another 4 subjects (18.18%). In group B in the first 24 hours fever was remitted in 9 patients (39.13%), after 48 hours in 9 patients (39.13%) and after 36 hours in another 5 subjects (21.73%).

After 3 days of antibiotic and symptomatic treatment thoracic pain, cough, expectoration, and dyspnea improved in 12 patients from group A (54.54%) and in 11 patients from B subjects (47.82%)

After 3 days of treatment with azithromycine 4 patients (18.18%) were still presenting subcrepitate rales. In group B, 5 subjects (21.73%) still had subcrepitant rales after 7 days of therapy with Augmentin BIS .

The radiological exam of the lungs performed after 10 days of monitoring demonstrated complete remission of the radiological signs in 13 subjects (59.09%) from the group A and in 12 patients (52.17%) from the group, with the remaining patients presenting a partial regression of lung radiological signs.

Within both groups, non-specific treatment included antalgics and antipyretics, expectorants, mucolytics, vitamins of the group B and C, while in some patients non-steroidic anti-inflammatory drugs were used.

None of the patient needed changes in the antibiotic therapy. Side effects recorded during the antibiotic treatment in both groups minor, transient and affected a small number of patients. (Table 2)

### Table 2. Therapeutic side effects in the two groups of study

<table>
<thead>
<tr>
<th>Secondary effects</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Percentage</td>
<td>No.</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>18.18%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>9.09%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3</td>
<td>13.63%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4.54%</td>
</tr>
<tr>
<td>Lingual candidosis</td>
<td>2</td>
<td>9.09%</td>
</tr>
</tbody>
</table>

### DISCUSSIONS

Clinical results obtained in the two groups demonstrate that both antibiotics are effective in treating the acute community-acquired pneumonia. Thus, good clinical outcome (successful therapy) was recorded in 21 patients (95.45%) from group A and in 22 (95.65%) from group B (without significant statistic differences between the two groups).

Therefore, both antibiotics can be recommended and successfully used in the empiric treatment of acute community-acquired pneumonia. We mention that in
the case of using azithromycin the compliance of the patients was higher (it is administered in a single daily dose), and the duration of the treatment and hospitalization is four days shorter compared to the classical therapy. Therefore, azithromycin appears to be cost-effective in the treatment of community-acquired pneumonia.

“Empiric” and early antibiotic treatment is essential and decisive in the majority of cases because any delay may lead to an increase in the mortality through community-acquired pneumonia with severe evolution.

Initially, antibiotics are given “empirical”, according to probability criteria, without awaiting upon results of the bacteriological exams, that may delay the antibiotic treatment.²

Arguments for an “empiric” initial antibiotherapy in community-acquired acute pneumonia are the following: 1. Etiology remains unknown in 30-50% of cases. 2. There are no predictive clinical and radiological criteria for a certain etiology. In 30% of cases with community-acquired acute pneumonia, clinical and radiological manifestations can not differentiate between alveolar and interstitial pneumonia. 3. No single antibiotic can cover the whole etiological array of the community-acquired pneumonia. 4. Bacteriological exam of the sputum offers in most situations, delayed and most of the time non-concludent results.³

French medical school considers that 80% of community-acquired acute pneumonia radiologically documented in adults without risk factors are produced by Streptococcus pneumoniae, Chlamydia pneumoniae and Mycoplasma pneumoniae. Therefore, these three etiological agents represent the main targets of the initial antibiotic therapy. The presence of risk factors requires to consider in the etiology staphylococcus and Gram negative bacteria.⁴

Both French and American medical schools consider that choosing the initial antibiotic therapy in the community-acquired acute must take into consideration the age of the patient, presence of risk factors (comorbidities) and of severity factors.⁵ ⁶

Evaluation of treatment efficacy must relay on the following elements: clinic and radiological evolution, disease severity, reactivity of the organism and the etiologic agent.⁷

Causes of a clinic and biological unfavorable outcome are multiple and can be grouped as follows: (1) Incorrect diagnosis of community-acquired acute pneumonia. In this case, the treating physician must include in the diagnosis algorithm other non-infectious lung disorders: congestive cardiac failure, lung embolic disease, atelectasis, sarcoidosis, bronchopulmonary neoplasm, irradiation pneumonia, drug-induced pneumonia, vasculitis, other inflammatory lung disorders. (2) Correct diagnosis of community-acquired acute pneumonia. In this situation, doctor must find the cause of failure in relation with reactivity of the organism, the antibiotics used or other resistance factors of the pathogen agent.⁸

**CONCLUSIONS**

Our study shows that clinical success observed in patients treated with azithromycin for 3 days is similar to that obtained after therapy with amoxycillin and clavulanic acid over a 7-day period.

Through its clinical and biological effectiveness, decreased frequency of adverse reactions and reduction of hospitalization period, with subsequently reduced hospitalization costs, azithromycin should be considered as first-line in the empiric treatment of patients with moderate infections of lower respiratory tract.

Through its large antibacterial activity, covering the most frequent germs involved in infections of respiratory tract, increased compliance, reduced period of administration and the availability for both ambulatory and in-hospital treatment in old patients and patients suffering from chronic diseases, azithromycin remains an efficient therapeutic alternative in the therapy of community-acquired moderate pneumonia.

**REFERENCES**