Clarithromycin – application paradigm, unsolved issues.

(Literature review and own observations)

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Macrolides are a well-known group of antibiotics, which recently has been used for the therapy of community-acquired respiratory infections. Their chemical structure is based on 14-15- or 16-membered lactonic ring.

The first macrolide antibiotic – erythromycin – was discovered in 1952. First it was used mainly for treatment of the infections, induced by Gram (+) bacteria, and as an alternative medicine in patients with penicillin allergy. Doctors still use it nowadays. After erythromycin a range of other macrolide antibiotics has been developed: spiramycin, josamycin and roxithromycin, as well as new macrolides, in particular – clarithromycin. The latest is characterized by better absorption compared to erythromycin, and longer half-life, it is more stable in acid medium and significantly more rarely causes undesirable reactions from the side of the gastrointestinal tract. Clarithromycin is a 14-membered macrolide; it is often used as a medicine or an alternative antibiotic for treatment of community-acquired respiratory infections.

The aim of this article is a critical review of experimental and clinical data on application of clarithromycin for infections of different localization.

Pharmacodynamics/pharmacokinetics of the medicine. Mechanism of the antimicrobial effect of clarithromycin is similar to other macrolides: reversible binding with 50S ribosomal subunit of a bacterial cell that leads to inhibition of the protein synthesis. The medicine is readily absorbed from the gastrointestinal tract, reaching maximum concentrations in 1 (250 mg) or 2 hours (500 mg) – 1 and 2.41 mg/L respectively; its bioavailability after oral administration is 55%. When different doses were administered, Cmax and AUC indices increased in proportion to the dose increase. Food intake does not significantly influence absorption of the medicine. Steady-state concentrations of clarithromycin in blood are created after the repeated administration of 5 doses. Clarithromycin Cmax in a steady-state stage are 1-1.5 and 2-3 mg/L after administration of 250 or 500 mg respectively. Accumulation of the medicine in blood is not observed after the repeated administration of a 200 mg dose twice a day for 14 days. Clarithromycin, as well as other macrolides, possesses low level of ionization and is soluble in lipids, for which cause it is distributed well in different organs and tissues. Volume of

clarithromycin distribution varies from 115 to 266 L, and binding with whey proteins varies from 42 to 70%.

Distribution of clarithromycin in the organism. ***Serum, tissues and extracellular fluids.*** It has been reported that clarithromycin reaches high concentration in the tissues and respiratory secretions that is of a big clinical importance. However, the following reasons point out the necessity to treat such statements very attentively. The peak concentration of erythromycin in the serum after its oral administration varies widely and depends on a drug form. The peak concentration of clarithromycin and its 14-hydroxymetabolite in the serum is lower, than that of erythromycin (1.1 mg/L compared to 2.9±0.8 mg/L respectively). Cmax of erythromycin and clarithromycin is lower than MIC90 for some significant causative agents of respiratory infections, including erythromycin-resistant pneumococci and *H.influenzae*. **Tissues**. It has been shown that the concentration of clarithromycin, formed in different tissues, in particular in tonsils, lungs, prostate gland and other genital organs, exceeds that of erythromycin, as well as it is higher than the concentration of the indicated antibiotic in the serum. The high concentration of clarithromycin in the tissues, however, is of a quite limited clinical importance. Their concentration was obtained in homogenizers of whole tissues, which mainly consisted of an intracellular material, and their high level was determined by a high intracellular concentration. The high concentration of the antibiotic inside the cells is important only for intracellular microorganisms and completely unusefull for extracellular causative agents, including the main respiratory pathogens - S.pneumoniae and *H.influenzae*. The key efficacy factor for extracellular causative agents is the concentration of antibiotic in the tissue fluid, which is in dynamic balance with the concentration in the serum, and is low in case of macrolides. The effectiveness of macrolides in respect toextracellular pathogens depends on extracellular concentration of an antibiotic and sensitivity degree of the microorganisms to it. The time, during which the concentration of a free extracellular antibiotic exceeds the MIC value, is the main factor, determining the effectiveness of macrolides. The high intracellular concentration of clarithromycin and azithromycin is caused by a pH-depending balance between ionized and non-ionized molecules. The molecules of macrolide antibiotics diffuse through the cell membranes in a non-ionized microbiologically active form, and when they reach the balance the concentration of non-ionized molecules is equal both inside and outside the cells. As a rule, the intracellular value of pH is lower, than the extracellular one, that is why the ionization inside the cells is higher. As a result, antibiotic accumulates inside the cells in an ionized from, which cannot diffuse and

is inactive. The amount of active antibiotic in the extracellular fluid decreases to a comparatively low level.

Epithelial lining fluids. Epithelial lining fluid (ELF) is a complex of biological fluids and inflammatory cells, which washes terminal bronchioles and alveoli. It is considered that clarithromycin reaches a comparatively high concentration (20-70 mg/L) in this fluid. However, determination of concentration in ELF is accompanied with a range of problems and, possibly, a true concentration of clarithromycin is considerably lower. The main difficulty in determination of antibiotic concentration in ELF is that when the method of bronchoalveolar lavage is used, phagocytes, existing in the fluid, are placed into an antibiotic-free medium. In this case, as a result of osmosis, any antibiotic, present in phagocytes, are released quickly. One of the *invitro* studies showed that considerable number of many antibiotics, present in phagocytes, can be excreted into the surrounding fluid within 20 min. Taking into account an artificial efflux of an intracellular antibiotic, it is possible that the given concentration of clarithromycin in the secretory fluid is considerably exaggerated, and the true value is too low to be of therapeutic importance. Unlike the concentration of clarithromycin in ELF, a corresponding concentration of azithromycin is extremely low. For instance, in two researches the concentration of azithromycin was lower than the resolution of the used method. Apparently, it has something to do with slower release of azithromycin from phagocytes in comparison to clarithromycin.

Middle ear fluid. It has been reported that the concentration of clarithromycin in the middle ear fluid (MEF) exceeds its level in the plasma (3.0-8.3 mg/L and 0.7-3.4 mg/L respectively). However, the problems that arise when the concentration of antibiotics in ELF is determined also spread on MEF. In the research, where a high concentration of clarithromycin was obtained, samples of MEF had been frozen under the temperature of -20° before the determination of the concentration of antibiotics. It caused the destruction of polymorphonuclear leucocytes, present in MEF, and the release of an intracellular antibiotic that influenced the concentration of free clarithromycin. Thus, now there is no strong evidence that the concentration of clarithromycin in MEF is higher than the expected one, obtained as a result of normal diffusion of an antibiotic from the serum. In the organism clarithromycin undergoes biotransformation with the production of the main metabolite – 14-hydroxy (R) clarithromycin, the production of which occurs to a greater degree than that of 14-hydroxy (S) epimer.

Is there any synergism between clarithromycin and 14-hydroclarithromycin? 14-hydroclarithromycin *invitro* in terms of activity is equal to erythromycin with

regard to *H.influenzae.* The suggestion was made that there is some synergism with regard to Haemophilus influenza between clarithromycin and its metabolite – 14-hydroxyclarithromycin, and thus, *invivo* activity of clarithromycin is higher than *invitro*. However, this hypothesis is based on the data of a research, the results of which, on close examination, are weak evidence to the statement of an enhanced activity. Synergism was observed with regard to only 50% of the studied *H.influenzae* strains. Besides, the curves of the bacterial destruction dynamics, given to support the synergism conception, are far from the truth. These curves show that clarithromycin (0.5 mg/L) in combination with 14-hydroxyclarithromycin (0.5 mg/L) caused bacterial destruction faster than clarithromycin (0.5 mg/L) or 14-hydroxyclarithromycin (0.5 mg/L) apart. Curves of bacterial destruction from clarithromycin or14-hydroxyclarithromycin in 1 mg/L concentration were not presented, thus, it is not possible to determine, whether these results reflect synergism or additive action. In the subsequent works, synergism between clarithromycin and its metabolite has not been proved either. It has been reported that the effect of two components in respect of *Kinfluenzae* is of additive character [27]. At the same time it was stated in the second publication that clarithromycin in combination with 14-hydroxyclarithromycin holds an intermediate position between clarithromycin and its metabolite according to their activity. Clarithromycin half-life after a single dose is 2.6-4.6 h; this indicator was higher for 14-hydroxyclarithromycin – 3.9-6.6 h. Total clearance of clarithromycin varies from 22 to 64 L/h. Renal excretion of clarithromycin is 18-36%, and that of 14-hydroxyclarithromycin is 9.6-12%. High concentrations of clarithromycin are found in the urine. Some amount of clarithromycin and the metabolite is excreted via faeces – 6.6 and 11.3%. Pharmacokinetics of clarithromycin in children at the age from 6 months to 10 years is similar to adults. In elderly people (65-84 years old) Cmax of clarithromycin and 14-hydroxyclarithromycin, as well as AUC, is considerably higher, and renal clearance is lower than in people aged 18-30. In patients with a severe renal dysfunction the increase in the indices of clarithromycin Cmax in blood and AUC prolongation T1/2, as well as the decrease of elimination rate constant, which correlated with a degree of renal failure, is observed. There are no significant changes in clarithromycin pharmacokinetics in patients with hepatic diseases, but some changes in Cmax indices and AUC of 14-hydroxyclarithromycin are observed. N case of severe renal failure (creatinine clearance is lower 1.8 L/h) it is recommended to reduce the dose or to increase the interval between the doses.

Post-antibiotic effect (PAE), i.e. retention of antimicrobial action of the drug after its removal from the medium, is characteristic for clarithromycin, as well as

all other macrolides. It is a result of irreversible changes in causative agent's ribosomes that lead to translocation blocking. Both clarithromycin and azithromycin possess a sub-MIC-postantibiotic effect – influence on microorganisms after effect of subinhibitory concentrations of an antibiotic. Under the influence of macrolide concentrations, even lower than MIC, microorganisms, including usually resistant ones (Pseudomonas aeruginosa), become more sensitive to the immune mechanisms of the macroorganism. It is connected with the fact that the ribosomal translocation can be blocked with small concentrations of the antibiotic.

All the macrolides possess **anti-inflammatory and immunomodulatory action.** Macrolides increase the activity of T-killers, accumulate in the neutrophils and macrophages, and enhance their phagocytic activity and migration to the focus of inflammation. Besides, they influence on oxidative reactions in the phagocytes and contribute to their degranulation, raise production of anti-inflammatory cytokine (interleukin-10) by monocytes, decrease production of proinflammatory cytokines by monocytes (interleukin-1, TNF±) and lymphocytes (interleukin-2), as well as that of inflammation mediators – prostaglandins, leukotrienes and thromboxanes. Anti-inflammatory action is evident even under sub-therapeutic concentrations of vacrolides and is similar to the effect of nonsteroidal anti-inflammatory drugs. Open prospective randomized research has been carried out to study the effect of clarithromycin on local and systemic inflammatory reaction. 54 women, who had undergone the mastectomy, have been examined for 16 months. The patients were divided into two groups. The test group received clarithromycin 500 mg a day, starting from the third day after the mastectomy. There was no significant difference in development of toxic reactions or surgical infection between the test and control group, but the treatment with clarithromycin led to the decrease of fever intensity, tachycardia, dyspnea and raised the level of monocytes ($P<0.0001$, <0.01, <0.05 and <0.01 respectively). Moreover, the intensity ($P<0.05$) and duration ($P<0.05$) of pain decreased, the range of motions in the shoulder joint for adduction and bending ($P<0.05$) increased. The researchers believe that clarithromycin is an effective anti-inflammatory drug. It is also necessary to note that clarithromycin, which does not influence tumors directly, recently has been described as an antineoplastic drug. Apparently, its mechanism of action is realized at the level of interleukins.

Tolerance and side effects. According to the summary data, given in the sum-up work, during the treatment of 4291 patients using clarithromycin, side effects were observed in 19.6% of cases, among them the most frequent were: nausea (3%), diarrhea (3%), dyspepsia (2%), abdominal pains (2%) and headache (2%). When

comparing the frequency of side effects under the use of clarithromycin and other macrolides (erythromycin, josamycin, roxithromycin), similar values were obtained – 15.7 and 19%; however, the reactions from GIT were observed truly rarer when clarithromycin was used (7.6 and 14%). The frequency of side effects under the use of clarithromycin and penicillins (penicillin, ampicillin, amoxicillin) was congruent (19.3 and 16.3%). Another review analyzes tolerance of clarithromycin in the controlled studies within the III phase that have been conducted in children of different age. Clarithromycin may contribute to the change of intestine biocoenosis. However, it gains clinical importance in very rare cases, when *Clostridiumdificille*-associated pseudomembranous colitis, diarrhea, vaginal or oral candidiasis are progressing.

Contraindications. ***Absolute:*** hypersensitivity of a slow type, pregnancy. ***Relative (risk/effect):*** breast feeding.

Interaction. ***Contra-indicated combinations:*** astemizole – terfenadine, linkosamides – chloramphenicol. ***Increase of serum concentration, toxic effect of:*** xanthines (except for difilin), carbamazepine, cyclosporine, valproic acid and indirect anticoagulants. The main reason for limited use of clarithromycin with other drugs is its interaction with cytochrome P450 (CYP3A4) system in the liver and enterocytes. Drug interaction of macrolides with drugs of a narrow margin of safety and that metabolize with CYP3A4 (carbamazepine, cyclosporine, terphenadine, asthemisol, cisapride and theophyllin) occur most frequently. It is recommended to avoid such combinations with regard to the increase of hepatoxicity risk or prolongation of QT interval with ventricular arrhythmia development. Risk of undesirable drug reactions rises in case of metabolism and drug clearance disorders (severe liver and kidney failure).

Combining. Combination of macrolides with other antibiotics may provide synergistic or additive action. Combination of b-lactams with high doses of macrolides is possible in an empiric treatment of severe community-acquired pneumonia and is aimed to “block” atypical agents, in respect of which b-lactams are ineffective. Combination of macrolides with lincosamides and chloramphenicol seems inadequate due to the identic mechanism of antimicrobial action. It is necessary to avoid competitive prescription of erythromycin with penicillin in cases when an immediate bactericidal effect of the latest is required (meningitis, septicaemia). Rifampicin, that is a part of treatment of *Mycobacteriumspp. and Legioellaspp.*-infections, together with clarithromycin enhances metabolism and significantly lowers serum concentration of the latest. A combined application of

macrolides is possible with: b-lactams, fluoroquinolones, aminoglycosides and rifampicin.

Antimicrobial spectrum of all the macrolides is identic. They are highly effective in respect of Gram-positive microorganisms and Gram-negative cocci, which are streptococcus, pneumococcus, meningococcus, gonococcus, treponema, clostridia, listeria, corynebacteria diphtheria, erythrasma and anthrax bacillus. Macrolides are effective against penicillinase-forming staphylococcus (except for methicillin-resistant one), enterococcus (partially), as well as some Gram-negative bacteria - Haemophilus influenza, Moraxella (Branchamella), Bordetella, Helicobacter, Borrelia and intracellular (atypical) microorganisms, such as legionella, chlamydia, mycoplasma, ureaplasma, gardnerella, coxiella and rickettsia. However, most Gram-negative microorganisms are naturally resistant to macrolides. Anaerobic bacteria are moderately sensitive to macrolides: clostridium, bacteroides, actinomycetes, propionibacteria, and anaerobic cocci. Atypical mycobacteria (M. avium, M. leprae) are sensitive to clarithromycin. Macrolides of the first generation (erythromycin, midecamycin) surpass the drugs of the II generation (except for clarithromycin) by action against Gram-positive microorganisms. Clarithromycin is superior to other macrolides, including erythromycin, azithromycin and roxithromycin by action on chlamydia, mycoplasma (M. pneumoniae), ureaplasma, legionella, staphylococci, streptococci, helicobacter, coxiella and bartonella. Clarithromycin is the most active medicine, used against atypical mycobacteria; in this regard it surpasses azithromycin 4 times.

The impact of pH on the antibiotic activity. The activity of clarithromycin decreases when pH medium lowers as a result of growth of their ionization and transformation into inactive forms. Clarithromycin sensitivity to pH may be of a great clinical importance, as pH of the middle ear, bronchi and lung tissue lowers during (and in the result of) the infection. For instance, in patients with acute otitis media (AOM) pH of the middle ear effusion is 6.5. Similar pH values are characteristic for endobronchial secretion in case of pneumonia. Influence of pH on the antimicrobial activity of macrolides is showed in vitro in the research on the effect of clarithromycin on H. influenzae. In the artificial models of the lung and middle ear effusion the clarithromycin activity and its 14-hydroxymetabolite in respect to H.influenzae lowered significantly, when pH decreased from 7.2 to 6.4. The activity of the control antibiotic (amoxicillin/ clavulanate) did not change, when pH lowered.

Clinical use. The multicenter studies showed that when clarithromycin was prescribed at a dose of 250-500 mg twice a day (not less than 5 days), the clinical

effect in acute bronchitis was observed in 97-99%, in acute chronic bronchitis – in 94-96%; from 106 patients with community-acquired pneumonia the clinical effect was observed in 105 (99%). Similar results of another multi-center study on clarithromycin effectiveness have been given: during the treatment of 965 patients with acute bronchitis, acute chronic bronchitis or pneumonia, the bacteriological effectiveness in infections, caused by most common causative agents (H.influenzae, S.aureus, S.pneumoniae), was 100%. The clinical effect was observed in 11121 (92%) patients out of 11143 patients, who had been administering clarithromycin at a dose of 250 (95%) or 500 mg (5%) twice a day in average for 6.7 days for treating lower (63%) or upper (26%) respiratory tract infections. In empiric clarithromycin treatment (intravenous or per os at a dose of 500 mg twice a day) of 78 patients with community-acquired pneumonia the effect was obtained in 97.5%, as well as in all 23 patients with mycoplasmal community-acquired pneumonia. There is data on a successful clarithromycin therapy for lower respiratory tract infections, caused by Chlamydia pneumonia, Mycoplasma pneumonia, Legionella pneumophila.

Numerous studies compared efficacy of clarithromycin and other antibacterial drugs in treatment of lower respiratory tract infections. The sum-up work gives the results of 17 publications on comparative efficacy of clerithromycin and other drugs in treatment of pneumonia, acute bronchitis and acute chronic bronchitis. It has been noted that clarithromycin at a dose of 250-500 mg twice a day within 1-2 weeks had the same clinical effect as josamycin and roxithromycin (100 and 150 mg twice a day) and erythromycin (250 or 500 mg 4 times a day) in treatment of patients with pneumonia, as well as ampicillin (250 or 500 mg 4 times a day), josamicin (500 mg 3 times a day), cefaclor (250 or 500 mg 3 times a day), cefuroxime axetil (500 mg twice a day), and cefixime (400 mg a day) in treatment of patients with acute bronchitis or acute chronic bronchitis.

Acute otitis media (AOM). In 60-70s erythromycin was approved for the treatment of AOM. High-potential results have been also obtained in a range of early clinical studies of azithromycin in AOM. However, increasing S.pneumoniae resistance to macrolides and frequent clinical ineffectiveness in the latest clinical studies limit the use of macrolides for treatment of this infection. ***Secretory otitis media.*** In theory the therapy of secretory otitis media using macrolide antibiotics involves the same problems, as in AOM. This has been demonstrated, when penetration of clarithromycin into the MEF in children with secretory otitis media was studied. The concentration in the middle ear exceeded the MIC values for most potential causative agents; however, eradication of H.influenzae wasn’t achieved in 47% of

children during the treatment. Besides, colonization of H.influenzae was observed in 50% of patients that had not had this agent before the antibiotic therapy.

In the therapy of 2015 patients with ***upper respiratory tract infections*** using clarithromycin at a dose of 250 or 500 mg twice a day for at least 5 days, recovery and improvement was observed in 85-95% of cases in acute pharyngitis, in 90-97% of cases in acute tonsillitis, in 87-96% of cases in acute sinusitis, in 96% of cases in laryngotracheitis, in 97% of cases in nonspecific upper respiratory tract infections. The summarized data shows that in case of streptococcal pharyngitis clinical and bacteriological efficacy of clarithromycin is almost equal to that of erythromycin and phenoxymethylpenicillin. In case of maxillitis the efficacy measures of clarithromycin (85-92%) were the same, as in the treatment with amoxicillin (independently or in combination with clavulanic acid).

Skin and soft tissue infections. The multicenter studies show that when clarithromycin was used at a dose of 250 mg twice a day the clinical effect was observed in 252 out of 266 patients with skin and soft tissue infections (95%), and the bacteriological effect – in 303 out of 330 patients (92%); clinical (96%) and bacteriological (92%) effect of the compared drugs (erythromycin at a dose of 250 mg 4 times a day or cefadroxil at a dose of 500 mg twice a day) were similar.

Genitourinary infections. According to the summarized data excellent and good clinical effects of clarithromycin were observed in 188 out of 204 patients with chlamydial urethritis (92%) and in 99 out of 116 patients with nonchlamydial nongonococcal urethritis (mainly ureaplasmatic); less pronounced effect was obtained in patients with combined (chlamydial and gonococcal) urethritis (55%) and urethritis, caused by gonococci (48%). Good results were obtained in women with cervicitis, caused by C. trachomatis (88%).

Infections in patients with ***immunodeficiency,*** caused by mycobacteria and toxoplasma. Clarithromycin was successfully used for the treatment of infections in patients with immunodeficiency, caused by Mycobacterium avium-intracellulare complex. When comparing the effectiveness of two doses of clarithromycin (500 and 1000 mg twice a day) in 83 patients with HIV infection and disseminated infection, caused by M.avium, no differences were detected in the patients' lifetime (404 and 337 days); this indicator was higher, than in similar patients, who received the combined therapy without clarithromycin (240-255 days), and it did not differ from the indicator in patients with HIV infection, but without M.avium contamination (330 days). Another study did not detct any differences in the clinical efficacy of two doses of clarithromycin in 469 patients with HIV infection and disseminated infection, caused by M.avium complex (79-85%); however, a

higher dose led to a bigger number of negative cultures after 10 weeks of the therapy (43 and 59%). Clarithromycin effectiveness in these infections was noted by other authors as well. Good results were obtained in the treatment of toxoplasmic encephalitis (common infection of the central nervous system in patients suffering from AIDS). Clinical success was observed in 80% of patients in case of the combined use of clarithromycin (1g twice a day) and pyrimethamine (75 mg a day) for 6 weeks (at 15% mortality rate).

Other infections. It is noted that use of clarithromycin together with omeprazole in patients with gastric ulcer causes more pronounced eradication of H.pylori (56-81%), than amoxicillin with omeprazole (29-30%).

Bronchial asthma. There is proof of interaction between chronic infection, caused by some intracellular pathogens, and such pathology, as asthma and chronic obstructive pulmonary diseases. According to the results of a double blind trial, published in Chest journal (2002), use of clarithromycin increases forced expiratory volume (FEV1) in patients suffering from bronchial asthma with a positive result of polymerase chain reaction (PCR) on Mycoplasma pneumonia or Chlamydia pneumonia. According to the researchers from National Jewish Medical and Research Center in Denver, Colorado, antibiotics may become an important addition to the therapy of some patients suffering from bronchial asthma. In 55 patients with medium heavy form of bronchial asthma the study of multiple tissue samples from the upper and lower respiratory tracts with a cultural method gave a negative result. However, PCR detected DNA of M.pneumoniae or C.pneumoniae in 31 patients (56%) from this group. Diagnostics of chlamidial and mycoplasmatic infections is quite difficult, and nowadays only few centers have the possibility to conduct all necessary analyses. That is why the scientists are developing easier methods of diagnostics for such infections. Before the start of antimicrobial therapy FEV1 was similar in patients with positive, as well as negative results of PCR. Without stopping a standard therapy for asthma, the patients were randomized into the group, receiving placebo, and the group, receiving 500 mg clarithromycin twice a day for 6 weeks. In patients with negative PCR results, who administered clarithromycin, significant changes in pulmonary function were not observed, while average FEV1 values in patients with positive PCR results increased by 200 ml. The researchers believe that this is a clinically significant improvement that is proved by the patients' subjective sensation. In spite of such improvement, probably connected with proinflammatory cytokine level reduction, the researchers do not recommend wide use of antibiotics for bronchial asthma treatment. Standard drug treatment for this disease is enough to control the symptoms of most patients, and the abuse of antibiotics leads to the

appearance of resistant microbial strains. Nevertheless, it is necessary to conduct analyses for bacterial infections in patients with bronchial asthma, which is resistant to the standard drug therapy, and to perform antimicrobial chemotherapy in case, if the lung infection is proved.

Sarcoidosis. The seroepidemiological data and the detected specific DNA, using PCR method, give evidence of a possible role of C.pneumoniae in sarcoidosis pathogenesis. It is quite interesting that the treatment of patients with acute sarcoidosis manifestations (arthritis, iridocyclitis, and cutaneous lesions) and a high titre of antibodies to C.pneumoniae with the application of glucocorticoids only was inefficient; and significant clinical improvement was observed after an additional prescription of macrolides.

Prophylactic application. Many macrolides may be used for prophylactic purposes. Erythromycin is used for pertussis prophylaxis in individuals, having been in contact with a sick person, and for sanation of carriers of B.pertussis; and in the second case erythromycin estolate is more effective, than ethylsuccinate and stearate. In a range of countries (France, Belgium etc.) a prophylactic prescription of spiramycin is recommended to individuals, having been in contact with patients, suffering from epidemic cerebrospinal meningitis. The researches are conducted on the evaluation of azithromycin effectiveness for the sanation of N.meningitidis carriers. In patients with penicillin allergy erythromycin may be used for year-round rheumatism prevention. For many years it has been considered as one of alternative antibiotics for the prevention of bacterial endocarditis in stomatology, otorhinolaryngology and urology. Such prophylaxis is necessary in patients with artificial cardiac valves, congenital and acquired heart diseases, hypertrophic cardiomyopathy, mitral valve prolapse with deficiency, provided there is bacteriological endocarditis in the medical history. According to the latest recommendations of the American Heart Association, erythromycin is not included into the group of such drugs any more, as its absorption in the intestine is variable and its pharmacokinetics is difficult to predict. Clarithromycin and azithromycin may be used as alternative antibiotics for endocarditis prevention before dental manipulations, bronchoscopy and esophagoscopy. Though, from the pharmacokinetic point of view, it would be more reasonable to recommend roxithromycin or spiramycin, as with their administration the concentrations in the blood serum are several times higher than the concentrations of azithromycin or clarithromycin.

Resistance of microorganisms to clarithromycin. The mechanisms of microbial resistance to macrolides are the following:

1. Modification of the target for action of ribosomal 50s-subunit (MLS-type). This process is catalyzed by enzymes – methylases. MLS-type resistance is not produced to 16-membered macrolides (midecamycin).

2. Efflux (emission) of an antibiotic from a microbial cell (Staphylococcus epidermidis has such an ability).

3. Inactivation of macrolides via decomposition of the lactonic ring by bacterial esterases or phosphotransferases. Chemical structure of semisynthetic macrolides preserves their lactonic ring from the destruction by enzymes. All the macrolides are ineffective in relation to microorganisms, naturally resistant to erythromycin. Acquired resistance to macrolides is developed quickly, but since the contact with antibiotic finishes, over the time sensitivity to it is restored. Intragroup cross-resistance of microorganisms to macrolides, in particular erythromycin, clarithromycin and azithromycin, is developed. Cross-resistance to macrolides is also observed in lincosamides. According to the results of the International multicenter research PROTEKT (2002), prevalence of S.pneumoniae, resistant to erythromycin, is 31.5% (from 12.2% in the UK to 36.6% in Spain and 58.1% in France). Methicillin-resistant strains of staphylococcus are resistant to all the macrolides. Unlike Gram-positive microorganisms (pneumococcus, streptococcus), development of resistance was not detected in Moraxella catarrhalis and atypical causative agents (mycoplasma, chlamydia, legionella). The risk of development of microbial resistance to azithromycin is higher, than to other macrolides of the II generation. Long-term persistence of azithromycin in the organism in low concentrations, which do not suppress the growth of microorganisms, but cause mutations, contributes to the resistance development. The situation with prevalence of macrolide-resistant pneumococci in Russia (apparently also in Ukraine) does not look so dramatic, as in a range of other countries. Thus, according to the data of the multicenter national research ПеГАС-I (phase B), when determining the sensitivity of 546 clinical S.pneumoniae strains, only 9% of them turned out to be resistant to erythromycin, clarithromycin and azithromycin. Resistance level of Helicobacter pillory to clarithromycin varies from 0 to 10% among adults, reaching 28% in children <5 years old that reflects more frequent use of macrolides in the youngest group. A good fact is that a combined use of macrolides with inhibitors of a proton pump restores sensitivity of previously resistant H.pilory strains in one third of cases.

Clinical data on application of clarithromycin for respiratory infections. The drug manifested a clinical efficacy in treatment of respiratory infections. In 16 controlled clinical trials the effect of clarithromycin in respiratory infections, in

which the microbiological activity was tested, the H.influenzae eradication rate was at the level of 54.5-100%. In this context macrolides (in particular azithromycin) occupy a prominent place in up-to-date manuals/recommendations on the management of patients with community-acquired lower respiratory tract infections. Thus, in particular, in the recommendations of the American Thoracic Society (ATS, 2001) and the Infectious Diseases Society of America (IDSA, 2000, 2003), macrolides are recommended as a drug of choice for treatment of nonsevere community-acquired pneumonia (CP), provided there are no so-called modifying factors, including concurrent diseases (diabetes mellitus, congestive cardiac failure, chronic bronchitis (CB)/chronic obstructive lung disease (COLD) etc.), other risk factors of drug resistance of S.pneumoniae (recent antibacterial therapy, old age etc.). Reasoned positioning of macrolides in CP therapy is based on a high antipneumococcal activity of drugs, activity in respect of atypical causative agents, as well as management of risk of drug resistance of pneumococcus. Thus, in the IDSA recommendations (2003), patients with nonsevere CP without concurrent diseases, who haven't received preceding antibacterial therapy, are recommended to administer macrolides or doxycycline, and in cases of preceding antibacterial therapy – respiratory fluoroquinolones (levofloxacin etc.) or (5-lactams in high doses (e.g. amoxicillin 1-3 times a day) in combination with "new" macrolides (azithromycin, clarithromycin). When nonsevere CP develops in individuals with concurrent diseases, who did not receive preceding antibacterial therapy, preference should be given to "new" macrolides or respiratory fluoroquinolones, and recent administration of antibiotics "modifies" treatment – monotherapy with respiratory fluoroquinolones or high-dose therapy with b-lactams in combination with "new" macrolides. According to the IDSA recommendations (2003), it is reasonable to prescribe the combined therapy, including b-lactam (cefotaxim, ceftriaxone, ampicillin/sulbactam, ertapenem) and a "new" macrolide, or the monotherapy with respiratory fluoroquinolone to the patients, hospitalized with CP.

At the present time, there is numerous evidence that in case of the combined prescription of b-lactams and macrolides for patients with CP, it is possible to optimize clinical outcomes of the disease (reduction of death risk, shortening of hospital stage of treatment) in comparison to the monotherapy with b-lactams. There is also proof that the combined therapy (b-lactam+macrolide) is more effective, than the b-lactam monotherapy, for treatment of severe pneumococcal pneumonia, complicated by secondary bacteriaemia. In a number of explanations of such "therapeutic synergism", apparently, it is necessary to take into account various effects of macrolides: suppression of the mixed infection and virulence

factors of causative agents, reduction of bacterial adhesion to the respiratory tract mucosa, lowering of production and improvement of flow properties of the bronchial secretion, immunomodulatory effect.

Domestic experts adhere to a similar approach in view of a role and place of macrolides in CP treatment (Ukrainian Ministry of Health order №311, 499).

AZICLAR drug (clarithromycin, FLAMINGO, India) is registered in Ukraine.

In the Department of Clinical Pharmacology and Pharmacotherapy the Institute of Therapy under the name of L.T. Malaya AMS, Ukraine, post marketing open clinical trial on the effectiveness of treatment of community-acquired pneumonia (CP) with Aziclar drug (clarithromycin, “Ananta Medicare”, UK) was conducted.

The aim of the research: study of clinical efficacy and tolerance of Aziclar drug in treatment of community-acquired pneumonia.

Justification of the trial: according to the order №499 of Ministry of Health, Ukraine, an antibacterial drug of choice for patients with CP of the first category is a macrolide antibiotic. In patients of the second Cp category macrolides are alternative drugs.

15 patients are involved into the trial (12 males and 3 females, an average age is 45.9±2.3 years) with the diagnosis: community-acquired pneumonia, I-II category, under the ambulatory treatment. CP was diagnosed on the basis of the criteria, approved by the order №499 of Ministry of Health, Ukraine. 11 patients had CP of the first clinical category, 4 patients had Cp of the second category. In the latest ones the sensitivity to b-lactam antibacterial drugs was increased anamnestically.

The research included patients of both sexes with clinically verified CP. Exclusion criteria were: 1) anamnestic indications on the intolerance of macrolide antibiotics; 2) administration of macrolides for last 3 months before the research; 3) refusal of treatment with clarithromycin; simultaneous application of other systematic antibacterial drugs; 4) patients with community-acquired pneumonia of the III-IV clinical category.

Clinical examination of the patients (complaints, physical examination) was conducted daily during the whole follow-up period. Determination of parameters of clinical blood and urine analysis, as well as bacteriological sputum examination was conducted during the inclusion period and on the 7^{th} day. X-ray examination of the chest organs was performed on the 1^{st} and 14^{th} day of the trial.

The studied drug was prescribed at a dose of 500 mg with a 12 hour interval with food. The antibacterial therapy was stopped 3 days after the normalization of a body temperature, but not more than 10 days of administration. The patient was moved to an alternative treatment regimen if there was no clinical improvement in the course of treatment after 3 days of clarithromycin administration.

The studied drug was effective (clinical and X-ray recovery from pneumonia occurred) in 14 patients (93.3%).

In one case clarithromycin was discontinued on the 5^{th} day of treatment because of the development of bitter taste in the mouth, heaviness in the right subcostal area, moderate increase of bilirubin level in the blood. The patient's status became stable on the 3^{rd} day after the studied drug had been replaced with gatifloxacin. Clinical cure of pneumonia in this patient occurred on the 7^{th} day of the therapy reverse, X-ray cure – on the 14^{th} day.

CONCLUSIONS

- Aziclar (clarithromycin) possesses a wide spectrum of antimicrobial activity that includes Gram-positive and Gram-negative microbes, atypical microorganisms and some anaerobes.
- Clarithromycin (Aziclar) shows higher in vitro activity, than erythromycin, in respect to a range of microorganisms, including B.melaninigenicus, C.pneumoniae, C.trachomatis, Legionella spp., Mycobacterium spp.
- Clarithromycin (Aziclar) has improved pharmacokinetic properties compared to erythromycin: better absorption from the gastrointestinal tract, forms higher maximum concentrations in the plasma, has a longer half-life, better penetration into the tissues. Due to the optimized pharmacokinetic properties, clarithromycin (Aziclar) may be used rarer (twice a day) and in lower doses (250-500 mg), than erythromycin.
- Nowadays a wealth of experience in clinical use of clarithromycin (Aziclar) has been accumulated. The drug may be regarded as a medication of the first row for treatment of community-acquired lower and upper respiratory tract infections, non-complicated skin and soft tissue infections in ambulance conditions. Clarithromycin (Aziclar) in combination with inhibitors of the proton pump (Panocid) and amoxicillin is a standard scheme of H.pylori eradication.
- It is possible to use the drug for pertussis prevention in individuals, having been in contact with a sick person.

- Clarithromycin is used for urogenital infections (chlamydiosis, mycoplasmosis, ureaplasmosis) in complex with fluoroquinolones (gatifloxacin) and tetracyclines.
- The data of the clinical trial of Aziclar (clarithromycin, “Ananta Medicare”, UK) indicates on 93.3% of efficacy and good tolerance of the drug in the treatment of patients with community-acquired pneumonia of the I-II clinical category.