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ORIGINAL RESEARCH

Use of immunomodulatory therapy as part of comprehensive treatment of non-severe community-acquired pneumonia and its long-term results

Mikhail P Kostinov[1,2], Vilia V Gainitdinova[1,2], Svetlana V Kazharova[1], Anna E Vlasenko[3], Vflentina B Polishchuk[1], Kirill V Mashilov[1]

[1]Federal State Budgetary Scientific Institution I.I. Mechnikov Research Institute of Vaccines and Sera, Moscow, Russia; [2]Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University (Sechenov University) of the MoH of the Russian Federation, Moscow, Russia; [3]Novokuznetsk State Institute of Advanced Medical Training – Branch of Federal State Budgetary Educational Institution of Additional Education 'Russian Medical Academy of Continuous Professional Education' of the MoH of the Russian Federation, Novokuznetsk, Russia

Abstract

Background: This study investigates the efficiency of two different types of immunomodulators for the treatment of non-severe community-acquired pneumonia (CAP) and assesses their long-term effects.

Methods: The study included 55 patients with non-severe CAP. Group 1 (control) received only standard CAP therapy; the other two groups received immunomodulators simultaneously with the standard therapy: bacterial lysate for group 2 and azoximer bromide (AzB) for group 3. TNF and IL-6 concentrations were determined on the day of hospitalization as well as on days 13 and 60 of follow-up. For 2 years, we monitored the incidence of low respiratory tract infections (LRTIs) in the same patients with CAP (n=55).

Results: The overall duration of all symptoms was lower in the immunomodulator groups compared with the control group. During treatment, TNF and IL-6 concentrations decreased on days 13 and 60 in all patients; in patients who received immunomodulators, TNF and IL-6 were reliably lower than in control patients. IL-6 concentration decreased on day 60 in the bacterial lysate and AzB treatment groups and did not differ (p=0.72). The odds ratio for the development of LRTIs in the AzB group was 0.15 (0.02–0.93) (p=0.04), suggesting its protective effect.

Conclusion: Inclusion of immunomodulators in the basic treatment of non-severe CAP reduces the duration of symptoms and is associated with improvement of the pro-inflammatory cytokine profile. In 2 years of follow-up, the long-term effects of the immunomodulatory therapy showed a statistically significant lower incidence of LRTIs in the AzB group only. However, given the small sample size of this study, further clinical studies are needed.

Keywords: azoximer bromide, bacterial lysate, IL-6, non-severe community-acquired pneumonia, TNF.

Citation

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Introduction

Community-acquired pneumonia (CAP) is a major issue in contemporary medicine, with a high incidence rate, a high mortality rate and significant expenses.[1–5] Decrease of non-specific body resistance, imbalance of local and systemic immunity, and free-radical oxidation abnormality substantially contribute to the pathogenesis of the disease.[6–9] Moreover, antibiotic-resistant strains are becoming more common, posing an additional threat because they can cause resistance to pathogenetic therapy.[10] This determines the need for an integrated approach to the treatment of CAP, including the use of immunomodulatory drugs.[11]

Cytokines are involved in many physiological and pathophysiological mechanisms of immunomodulation, and they are amongst the main activators of the functional activity of phagocytic cells. However, an excessive increase in the production of pro-inflammatory cytokines is dangerous for the body because these mediators can cause severe pathological processes such as septic shock.[12]

Azoximer bromide (AzB) stimulates monocyte–macrophage cell and natural killer cell activation, which results in strengthening of the functional activity of both cell-mediated and humoral immunity. A prolonged effect is also under discussion.[13] Thus, AzB has successfully been used in the complex treatment of a number of acute and chronic infectious processes.[12]

According to clinical trials, most immunomodulatory drugs based on bacterial lysates (BLs) have been demonstrated to have high safety and to reduce the severity of respiratory tract infections (RTIs). In some cases, the use of immunomodulators made it possible to reduce the number of prescribed antibiotics.[10] Dendritic cells recognize bacterial antigens in these preparations, triggering an immune response and the production of B cell antibodies as well as the production of macrophages, polymorphonuclear neutrophils, lysozymes and the secretory component of IgA (SIgA), increasing immune resistance.[6,7,14,15]

Recurrent RTIs in adults, which occur due to an imbalance between lung defence mechanisms and bacterial load, continue to be one of the most pressing public health problems. Antibacterial treatment can temporarily restore this lost balance but does not prevent the infection from recurring. An alternative approach to the prevention of recurrent infection is the inclusion of immunomodulators in the complex treatment of RTIs, which provides immune protection against repeated bacterial and viral infections.[14,16–18]

To date, studies examining the effectiveness of immunomodulatory therapy in CAP in the acute and long-term periods are very few.[19] Our work aimed to study the effectiveness of two different types of immunomodulators for the treatment of non-severe CAP and assess the long-term effects of the treatment conducted.

Methods

The Local Ethics Committee of the Research Institute of Pulmonology approved this randomized controlled trial on September 15, 2016. The study was conducted under the Declaration of Helsinki, the International Council for Harmonization Guidelines for Good Clinical Practice, and Russian regulatory requirements. We conducted the study in the following clinics: City Clinical Hospital No. 57 (Moscow), City Clinical Hospital No. 1 (Nalchik) and Republic Clinical Hospital of the Kabardino-Balkarian Republic (Nalchik).

Ethics approval and consent to participate

The study was based on the ethical principles and recommendations of the WHO and the Russian Ministry of Health. All patients signed informed consent for participation in the study before the beginning of the research.

Patients

The study included adult patients (n=55) with non-severe CAP. We conducted diagnosis and treatment according to the Federal Clinical Guidelines 'Community-acquired Pneumonia in Adults — 2021–2022–2023' (08.25.2021), which divides CAP into non-severe and severe CAP according to the severity of the course. Unlike the non-severe form, severe CAP is associated with rapid progression of disease symptoms, higher clinical failure and high mortality. Such patients require urgent admission to the ICU. The American Thoracic Society/American Society for Infectious Diseases (ATS/ASID) CAP guidelines and the SMART-COP scale and its modifications were used to identify individuals with severe CAP.

Non-severe CAP was diagnosed based on clinical objective findings (at least two criteria of the following): fever ≥38°C, cough with sputum, physical findings (shortening of percussion sound, focus of crepitation and/or small bubbling rale, harsh bronchial breathing), leukocytosis of more than 10×10^9, and/or left shift of more than 10% and proved by X-ray examination (presence of focal pulmonary infiltrates in no more than one lung segment). We used the CRB-65 scale to assess CAP severity and included patients with score <1, corresponding to non-severe course of disease to be treated in the outpatient setting.[1,2]

Inclusion criteria

All patients with non-severe CAP, aged 18–60 years, who volunteered and were able to comply with the requirements of the protocol, and provided written informed consent to participate in a clinical trial were included.

Exclusion criteria

The exclusion criteria were as follows: infiltration of lung tissue in more than one segment of the lung; severe forms of concomitant respiratory diseases (bronchial asthma, chronic obstructive pulmonary disease, bronchiectasis, lung abscesses, pleural empyema, active tuberculosis); severe non-pulmonary concomitant conditions (chronic heart failure, diabetes mellitus, chronic renal and he-

patic failure, viral hepatitis B and C, malignant tumours, immunodeficiencies); volunteers who received immunoglobulin-containing drugs or blood transfusion within the last 3 months before the study; long-term use (more than 14 days) of immunosuppressants or other immunomodulatory drugs during the 6 months preceding the study; chronic alcohol abuse and/or drug addiction; pregnancy and lactation; non-compliance by the patient with the protocol; or refusal of the patient to continue participation in the study.

A total of 55 people were included in the study. Using simple randomization, we divided the patients into three groups: group 1 (control, *n*=15) received no immunomodulating drugs and only standard therapy (antibacterial and supportive) according to the Clinical Guidelines 'Community-acquired Pneumonia in Adults' of the Ministry of Health of Russia. Standard therapy involved comprised amoxicillin (orally) 1000 mg twice daily for 7 days, paracetamol 500 mg for fever, lazolvan (orally) 30 mg twice daily or acetylcysteine 600 mg/day for 7 days, berodual inhalation through a nebulizer (10–14 days), and plenty of fluids. Group 2 (*n*=20) received, in addition to standard therapy, BL (Broncho-Vaxom, OM Pharma SA, Switzerland) 7 mg OD, one cycle of 30 days followed by two cycles of 10 days, each with an interval of 20 days. Group 3 (*n*=20) received, in addition to standard therapy, AzB (Polyoxidonium, NPO Petrovax Pharm LLC, Russia) 6 mg IM OD every day for 3 days, then every other day (10 injections per course). Immunomodulating agents were prescribed simultaneously at the start of standard therapy; the prescription was made considering indications and contraindications according to the instructions for use. None of the patients were aware of the type of therapy they were receiving. The control group was represented by a group of 20 healthy individuals comparable to the study groups in terms of age, comorbidities, BMI and smoking history.

We analysed the overall duration of CAP and the duration of each symptom separately in all patients. Patients recorded symptoms and filled in a proforma table themselves daily.

Criteria of convalescence were stable fever relief to <37.2°C for at least 48 hours; absence of toxic syndrome (fatigue, excessive sweating); respiration rate <20/min (in patients without chronic respiratory distress); absence of purulent sputum (except for patients with its permanent production); WBC count $<10\times10^9$/L, neutrophils <80% and immature forms of neutrophils (metamyelocytes) <6%.[2]

The duration of CAP was evaluated as the maximum duration of each of the recorded symptoms. Based on a review of published data (considering inclusion and exclusion criteria), the expected reduction in CAP duration would be of 4.35 (5.18–3.52) days.[20,21] We calculated the estimated effect size for the analysis of the three study groups to be f=0.44,[22] with appropriate recalculations. The sample size relevant to this effect value was equal to 54 patients in total, 18 in each group.[23]

All patients underwent assessment of demographic indices, smoking intensity, BMI, symptoms, data of physical examination, laboratory and instrumental examination (complete blood count, biochemical blood test, sputum culture, X-ray imaging (or computed tomography)) of thoracic organs on the day of hospitalization. We analysed concomitant diseases based on electronic medical records.

CAP severity was assessed using the CRB-65 scale (impairment of consciousness, respiration rate, systolic blood pressure <90 mmHg or diastolic blood pressure ≥60 mmHg, age ≥65 years). We included patients with a score of <1 in the study.

Serum/plasma cytokine concentrations (TNF and IL-6) were measured on the day of hospitalization (day 1) and on days 13 and 60 of follow-up. Blood samples were taken from the basilic vein, the serum was separated by centrifugation (3000 rpm) and the samples were frozen until required for the study.

TNF and IL-6 levels were determined using sandwich ELISA with specific reagents from R&D Diagnostic Inc., USA. The optical density was determined on a Multiscan Ascent microplate immunoenzymatic photometer (Thermo Electron Corporation, Finland).

Certified equipment of the Research Equipment Sharing Center of the Federal State Budgetary Scientific Institution I.I. Mechnikov Research Institute of Vaccines and Sera was used in this work.

After recovery, we followed all patients for 2 years. During this time, the incidence of acute respiratory diseases was assessed. The number of cases of acute respiratory disease was recorded based on interviews (the patients under follow-up were called every 3 months) and as documented evidence as an entry in medical history. The long-term effect of immunomodulatory therapy was assessed in the same three groups of patients.

Statistical analysis

Values of biomarker concentration were presented as mean ± standard deviation (M±SD) and change from baseline was presented by a median and interquartile range expressed as a percentage change from baseline. To compare two unlinked samples by quantity, the

Mann–Whitney *U* test was used; to compare three unlinked samples, the Kruskal–Wallis *H* test was used with the Steel–Dwass *post-hoc* comparison test. Three and more dependent samples (one group in different points of time) were compared using the Friedman test, and where statistical significance was reached at $p \leq 0.05$, pairwise comparisons using the Nemenyi *post-hoc* test were performed.

The difference in the duration of given symptoms in each study group was assessed using the Kaplan–Meier estimator and the log-rank test; the median time until symptom disappearance (with indication of 95% CI) and the difference between the median time of symptom duration in the various groups was calculated with the use of Hodges–Lehmann estimators was presented.

The inter-relation between the treatment regimen and the incidence of respiratory diseases within 2 years after CAP (expressed in terms of 1000 person days) was analysed using Poisson regression with the incidence risk ratio and corresponding 95% CI. Both single-factor and multifactor models considering patient sex and age were calculated.

To analyse the inter-relation of immunomodulatory therapy and the probability of repeated low respiratory tract infection (LRTI) within 2 years after CAP, a multifactor logit regression (adjusted for patient sex and age) with an odds ratio and its 95% CI calculation was applied.

For qualitative attributes, absolute and relative (%) ratios were found. Two groups were compared by qualitative nominal parameters during cross-tabulation analysis with χ^2 test (Fisher's exact test in cases of expected frequencies ≤5%).

The differences were regarded as statistically significant at $p \leq 0.05$. GraphPad Prism (v.9.3.0 License GPS-1963924) and the statistical environment R (v.3.6, License GNU GPL2) were used for calculations and the construction of graphs.

Results

All patients (n=55) in the study had clinical signs of non-severe CAP such as cough, toxic shock syndrome and syndrome of general inflammatory changes (feeling hot, chills, fever, changes in acute-phase blood parameters: leukocytosis, neutrophilic shift, increased ESR, fibrinogen, α2-globulins and the appearance of C-reactive protein). Clinical-laboratory and instrumental characteristics of patients included in the study are presented in Table 1. Study groups were comparable by all characteristics under analysis.

Cough, fatigue and crepitation were recorded in all 55 patients; fever was noted in 53 (96%) patients; 44 (80%) patients (11 in control group, 16 in BL group and 17 in AzB group; p=0.69) had excessive sweating; 43 (78%) patients (11 in control group, 15 in BL group and 17 in AzB group; p=0.65) noted shortness of breath during normal exercise; 32 (58%) patients had pain in the chest; 21 (38%) patients had headache; 14 (25%) patients felt palpitation; 18 (33%) patients had chills; and 22 (40%) patients (8 in control group, 8 in BL group and 7 in AzB group; p=0.91) noted cough with mucopurulent and purulent sputum. Pulmonary tissue consolidation syndrome, discomfort when breathing, and shortness of breath were also observed.

Clinical analysis of peripheral blood in patients receiving immunomodulators at admission revealed statistically significant changes characteristic of the inflammatory process. On the 13th day of follow-up in these groups, there was a pronounced tendency to normalize these indicators: moderate leukocytosis with a shift to the left (10.3 (8.8–11.7) *versus* 5.2 (4–6.4); p<0.001), monocytosis (5.4% (4.4–6.1) *versus* 4.8 (3.6–5.8); p=0.03) and increased ESR (27.4 (22.3–34.6) *versus* 5.6 (4.2–7.1); p<0.001). There were no significant changes in the parameters of the clinical blood test in patients who did not receive immunomodulators.

The Kaplan–Meier method was used to assess the immunomodulatory therapy effect on the duration of certain symptoms and the overall CAP duration. The overall duration of all symptoms (duration of illness) was shorter in immunomodulator groups (12 (11–13) days in BL group (p<0.001) and 12 (11–12) days in AzB group (p<0.001)) than in the control group (14 (13–15) days); furthermore, the intervention groups were not statistically significantly different from each other (p=0.36) (Figure 1a). Durations of shortness of breath (p=0.59), crepitation (p=0.07) and excessive sweating (p=0.11) were not statistically significantly different between study groups.

The duration of asthenia (fatigue) was statistically significantly shorter in the groups treated with immunomodulators than in the control group (13 (12–14) days *versus* 10 (9–11) days in the BL group (p=0.004) and 10 (9–11) days in the AzB group (p=0.001)); the immunomodulator treatment groups were not statistically significantly different from each other (p=0.69) (Figure 2b).

Cough with sputum is of particular note: in both immunomodulator treatment groups, the duration of this symptom was shorter than in the control group (1 (0–3) day in BL group (p=0.03) and 2 (1–4) days in AzB group (p=0.002)), and the duration of cough with sputum in the

Table 1. Clinical and laboratory and instrumental characteristics of patients with community-acquired pneumonia.

Indicator	Total	Study groups			*p* value[a]
		Control (*n*=15)	BL (*n*=20)	AzB (*n*=20)	
Age, years old	41 (31–48)	41 (31–48)	41 (31–49)	40 (31–48)	*p*=0.88
Men/women	33/22	10/4	12/8	11/10	*p*=0.38
Smoking index, pack/years	10 (10–15)	10 (10–15)	10 (10–14)	11 (9–14)	*p*=0.80
CRB-65, scores	0.15 (0.1–1)	0.15 (0–1)	0.16 (0–1)	0.14 (0–1)	*p*=0.78
BMI, kg/m^2	21 (19–22)	21 (19–22)	21 (20–22)	21 (18–22)	*p*=0.74
Respiratory rate, min	18 (17–18)	18 (17–18)	18 (17–18)	18 (17–18)	*p*=1.00
SpO_2, %	96 (96–97)	96 (95–97)	96 (96–97)	96 (96–98)	*p*=0.49
Heart rate, min	74 (70–76)	74 (70–82)	74 (70–76)	72 (71–82)	*p*=1.00
SBP, mmHg	120 (110–128)	120 (100–130)	120 (112–128)	118 (100–130)	*p*=0.96
DBP, mmHg	78 (76–82)	80 (78–84)	78 (72–82)	78 (76–83)	*p*=0.13
WBC, ×10^9 /L	10.3 (8.8–11.7)	10.0 (8.9–10.6)	10.8 (8.7–11.6)	11.3 (8.8–11.9)	*p*=0.49
Total protein, g/L	63 (59–65)	63 (59–65)	63 (61–65)	63 (59–65)	*p*=0.77
Creatinine, μmol/L	78 (73–84)	78 (71–83)	81 (73–85)	78 (72–84)	*p*=0.37
Cholesterol, mmol/l	4.7 (4.3–5.7)	4.6 (4.3–5.3)	4.9 (4.2–6.2)	5.1 (4.3–6.2)	*p*=0.57
Glucose, mmol/L	5.2 (4.8–5.9)	4.9 (4.5–5.9)	5.6 (4.8–5.9)	5.2 (4.8–6.1)	*p*=0.55
CRP, mg/mL	23 (9–36)	16 (6–33)	27 (12–37)	23 (7–35)	*p*=0.36
Duration of illness from baseline, days	4 (3–6)	4 (3–6)	4.5 (3–6)	4 (3–6)	*p*=0.89

[a]The Kruskal–Wallis test was used.
AzB, azoximer bromide; BL, bacterial lysate; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpO_2, blood oxygen saturation.

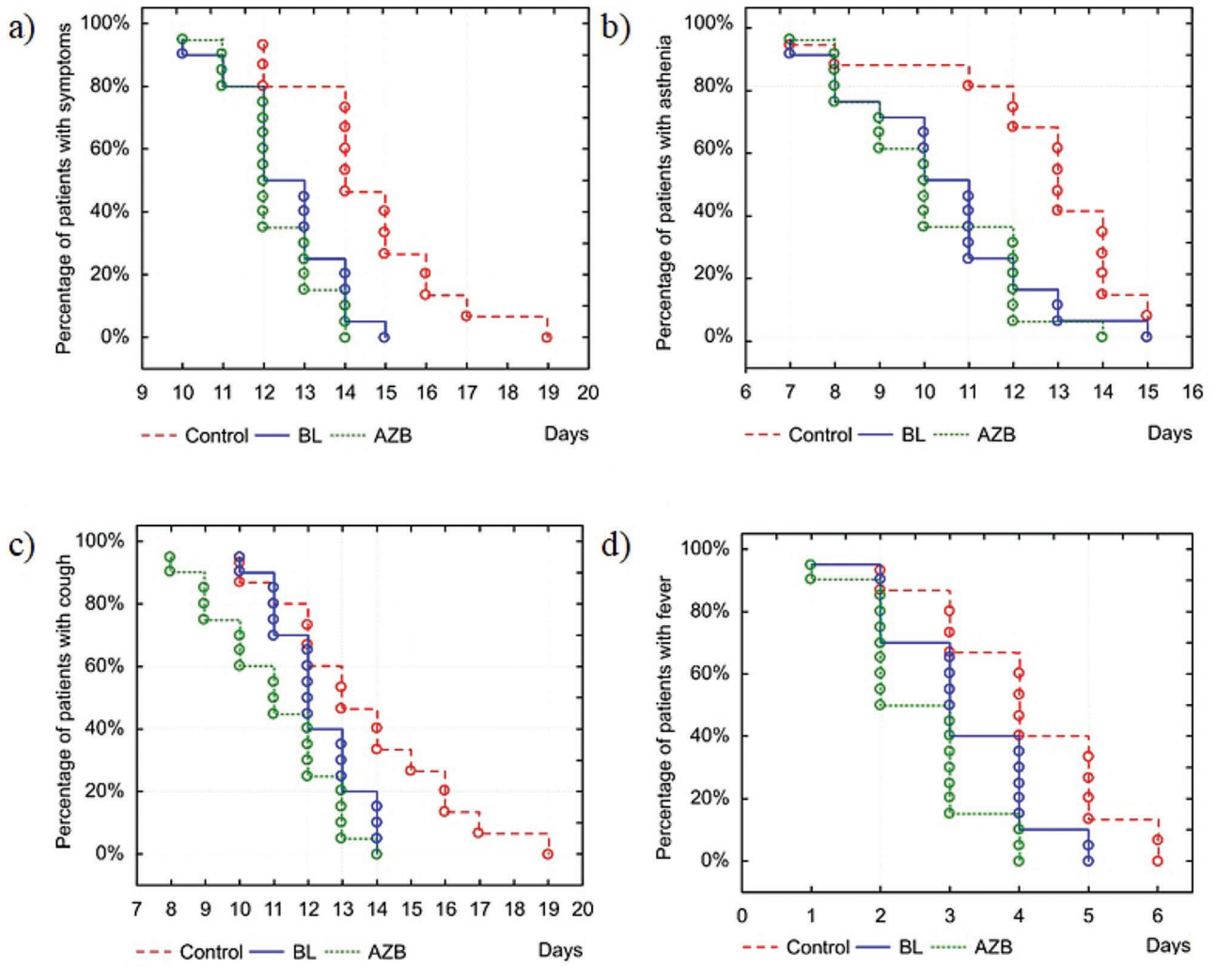
AzB treatment group was shorter than in the BL treatment group (11 (10–12) days *versus* 12 (11–13) days (*p*=0.05) (Figure 1c). Similar results were observed with fever: in the BL group, the duration of this symptom was shorter than in the control group (3 (2–4) days *versus* 4 (3–5) days (*p*=0.02)), but the shortest fever duration was in the ABZ treatment group: 2 (1–3) days (*p*<0.001 *versus* control and *p*=0.05 versus BL treatment group) (Figure 1d).

The effect of immunomodulators on the acute inflammatory phase markers TNF and IL-6 was analysed. On the first day of observation, TNF and IL-6 values (Table 2) were comparable between all groups and statistically significantly exceeded the TNF and IL-6 concentrations in the healthy donors group (2.2±0.24 pg/mL and 1.4±0.19 pg/mL, respectively; *p*<0.001 in both cases).

On day 13 of treatment, a statistically significant decrease in TNF and IL-6 levels in all groups compared with baseline level was revealed (in control group, *p*=0.03 for TNF and *p*=0.04 for IL-6; in study groups, *p*=0.01 in each case). Decreases in TNF and IL-6 levels were statistically significantly more pronounced (as compared with the group of patients without immunomodulators) in patients who received BL (up to 13.7±3.4 pg/mL; by 44% (-64 to -32) from baseline (*p*=0.004) for TNF and 22.8±3.6 pg/mL; by 32% (-40 to -18) (*p*=0.007) for IL-6) and those who received AzB (up to 14.8±2.9 pg/mL; by 45% (-53 to -38) (*p*=0.02) for TNF and 23.5±3.8 pg/mL; by 28% (-40 to -20) (*p*=0.004) for IL-6). In the control group, TNF concentration decreased by 18% (-32 to -8; to 19.5±2.3 pg/mL) and IL-6 concentration by 11% (-20 to -1; to 28.3±3.2 pg/mL).

On day 60 of the study, a further statistically significant decrease in TNF and IL-6 levels was revealed in all groups. The lowest indicators of the biomarkers determined (that were also statistically significantly different from the control) were revealed in patients who received BL and AzB (*p*=0.001 in both cases).

Figure 1. Kaplan–Meier curves for the time from the start of treatment to the disappearance of non-severe community-acquired pneumonia symptoms.



Comparison of TNF and IL-6 decrease over time between all groups on day 60 of the study compared with the baseline showed a decrease of 85% (-89 to -82) and 86% (-90 to -85), respectively, in the BL treatment group, and of 82% (-86 to -80) and 86% (-88 to -84), respectively, in the AzB treatment group. In the control group, the decrease in TNF and IL-6 concentrations was of 64% (-78 to -56) and 75% (-81 to -74), respectively, which statistically significantly differs from the BL group ($p<0.001$ for TNF and $p=0.001$ for IL-6) and AzB group ($p=0.002$ for TNF and $p=0.007$ for IL-6). In the BL group, on day 60 of observation, the dynamic decrease in TNF concentration was a bit higher than in the AzB group but without any statistically significant differences ($p=0.24$) (Figure 2a). The degree of IL-6 concentration decreases on day 60 was the same in BL and AzB groups ($p=0.72$) (Figure 2b).

Finally, the long-term effect (2 years) of immunomodulatory therapy on the incidence of LRTIs (acute bronchitis, exacerbation of chronic bronchitis, CAP) in patients with previous CAP infection was analysed. The incidence of such diseases over the 2 years of observation was 47% ($n=7$) in the control group, 30% ($n=6$) in the BL treatment group ($p=0.31$ *versus* control) and 10% ($n=2$) in the AzB treatment group ($p=0.02$ *versus* control). Sex-adjusted and age-adjusted odds ratio for the development of LRTIs (during the 2 years after CAP) in the AzB treatment group was 0.15 (0.02–0.93) ($p=0.04$), suggesting its protective effect (Figure 3).

Discussion

Our study revealed the clinical effectiveness of the use of immunomodulators in the course of mild CAP.

Table 2. TNF and IL-6 concentrations at baseline and over time during treatment in comparison groups, M±σ.

Study groups	Change of indicators, M±σ			Comparison over time[a]
	Day 1	13 days	60 days	
TNF, pg/mL				
1. Control (N=20)	26.0±5.1	19.5±2.3	8.0±2.9	$p<0.001$: $p^{13}=0.03$, $p^{60}<0.001$
2. BL (N=20)	26.5±3.7	13.7±3.4	3.8±1.2	$p<0.001$: $p^{13}=0.01$, $p^{60}<0.001$
3. AzB (group 3, N=20)	26.6±4.7	14.8±2.9	4.4±1.2	$p<0.001$: $p^{13}=0.01$, $p^{60}<0.001$
Comparing groups[b]	$p=0.71$	$p<0.001$: $p^{1/2}<0.001$, $p^{1/3}<0.001$, $p^{2/3}=0.65$	$p<0.001$: $p^{1/2}<0.001$, $p^{1/3}<0.001$, $p^{2/3}=0.33$	
IL-6, pg/mL				
1. Control (N=20)	32.7±6.4	28.3±3.2	7.2±1.5	$p<0.001$: $p^{13}=0.04$, $p^{60}<0.001$
2. BL (N=20)	32.7±4.1	22.8±3.6	4.2±1.2	$p<0.001$: $p^{13}=0.01$, $p^{60}<0.001$
3. ABZ (group 3, N=20)	33.2±3.4	23.5±3.8	4.8±1.6	$p<0.001$: $p^{13}=0.01$, $p^{60}<0.001$
Comparing groups[b]	$p=0.77$	$p<0.001$: $p^{1/2}<0.001$, $p^{1/3}<0.006$, $p^{2/3}=0.85$	$p<0.001$: $p^{1/2}<0.001$, $p^{1/3}<0.001$, $p^{2/3}=0.56$	

[a]The Friedman test was used, and in case of its statistical significance at $p\leq0.05$, pairwise comparisons using the Nemenyi *post-hoc* test were conducted, where p^{13} and p^{60} are the statistical significances of changes on days 13 and 60 of the study, respectively, as compared with baseline (day 1 of the study).
[b]The Kruskal–Wallis test was used; in case of its statistical significance at $p\leq0.05$, pairwise comparisons were conducted using the Steel–Dwass *post-hoc* comparison test, where $p^{1/2}$, $p^{1/3}$ and $p^{2/3}$ are the statistical significances of differences between groups BL and control, AzB and control, and BL and AzB, respectively.
AzB, azoximer bromide; BL, bacterial lysate.

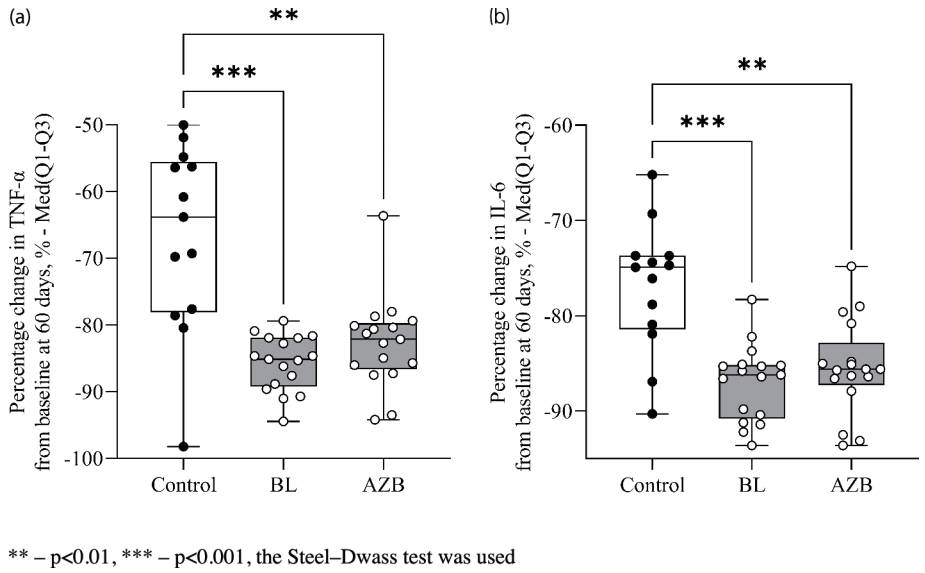
In outpatient settings, pneumonia is diagnosed based on the results of the following or two events: acute onset fever ≥38.0°C, cough with sputum, probably unproductive, and physical signs of infiltration in lung tissue (crepitation, wheezing, bronchial breathing, dulling percussion).[1] Patients with pneumonia often complain of unmotivated weakness, fatigue and increased sweating at night.[2,10,24]

Pneumonia is an inflammatory and destructive disease of the bronchopulmonary tissue. Inflammation, including CAP, develops in response to the spread of pathogens in tissues with the participation of pro-inflammatory cytokines.[11] The most important pathogenetic factors of the inflammatory process are not only disorders of innate and adaptive immunity but also circulatory disorders in lung tissue as well as microcirculation disorders in focal manifestations. Circulatory disorders at various levels lead to circulatory and tissue hypoxia.

The inflammatory process in pneumonia is accompanied by oxidative stress and an increase in the concentrations of pro-inflammatory cytokines such as TNF and IL-6 in the blood plasma. At the same time, the use of an antioxidant, such as ascorbic acid, leads to a decrease in these concentrations.[25]

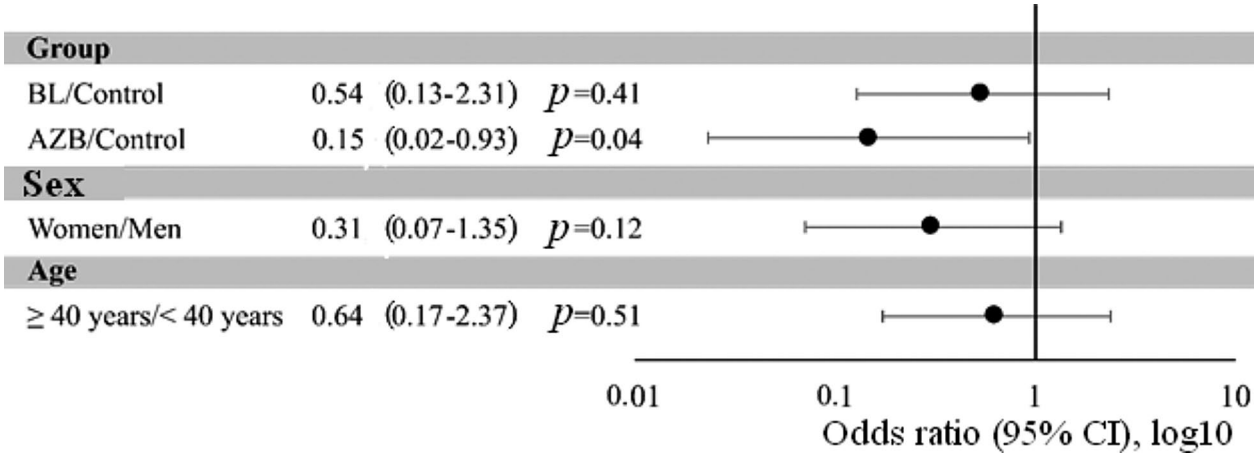
An increased level of TNF is associated with an increased likelihood of complications, adverse effects and rapid deaths. At the same time, some authors note that the initially low TNF level reduces the resistance of the host organism against *Streptococcus pneumoniae*, having little effect on the condition of lung tissue.[26]

Figure 2. Percentage change in TNF (a) and IL-6 (b) from baseline during treatment in comparison groups at 60 days.



** – p<0.01, *** – p<0.001, the Steel–Dwass test was used

Figure 3. Odds ratio for the development of low respiratory tract infection within 2 years after CAP, a multifactor logit regression model was used: group + sex + age.



In pneumonia, many authors note an increase in the level of several cytokines (IL-10, IL-4, IL-6, IL-8, IL-1α, IL-1β and TNF), the severity of which depends on the extent of disease and nature of the pathogen.[27–29] The most accurate biomarker of pneumonia is IL-6.[30] The same biomarker of the course of pneumonia can be considered the level of TNF. Thus, the significant decrease in the levels of IL-6 and TNF observed herein is an indirect but objective sign of a decrease in the severity of the disease and an improvement in the prognosis of its outcome.

Similarly, we can state that both drugs have approximately the same efficiency, despite the completely different composition and mechanism of action. Significant differences in the effect of drugs appear only in the analysis of long-term results of treatment. We found that, during the 2 years of follow-up, the incidence of lower respiratory tract infections in patients treated with AzB was significantly lower. Perhaps this can be explained by the more versatile action of AzB, which not only has immunotropic activity but also pronounced detoxifying and antioxidant properties.[13,31] It can also be assumed that the observed effect of AzB on the level of cytokines (primarily TNF) in pneumonia is due to these features, which contribute to the active suppression of the inflammatory process. This assumption is indirect-

ly confirmed by the fact that, when correcting irritable bowel syndrome with probiotics, the addition of AzB to the treatment regimen also leads to a significant decrease in the content of TNF.[32]

Conclusion

Thus, the inclusion of immunomodulators in the basic therapy of non-severe CAP leads to a decrease in the duration of symptoms and is associated with an improvement in the cytokine profile, whilst Broncho-Vaxom (BL) and Polyoxidonium (AzB) showed approximately the same therapeutic efficacy. The long-term effects of immunomodulatory therapy showed a statistically significant reduction in the incidence of lower respiratory tract infections in the AzB group during the 2 years of follow-up; however, given the small sample size of this study, further clinical studies are needed.

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Correspondence: Kirill Vadimovich Mashilov, Mechnicov Institute of Vaccines & Sera, Small Kazeny lane 5a, Moscow, Russian Federation. Email: k.v.mashilov@gmail.com

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