

ORIGINAL RESEARCH

The effect of azoximer bromide (Polyoxidonium®) in patients hospitalized with coronavirus disease (COVID-19): an open-label, multicentre, interventional clinical study

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Abstract

A clinical need for aetiologic coronavirus disease (COVID-19) treatments is required. The immune modulator azoximer bromide (AZB; Polyoxidonium®) is indicated in Russia for use against acute viral infections and during remission. In this study, adults hospitalized with COVID-19 ($n=32$) received AZB and standard of care in an open-label, multicentre, interventional study. All patients were symptomatic; 22 had severe disease (National Early Warning Score ≥ 5) and required mechanical ventilation or respiratory support and 19 patients had co-morbidities. Patients received AZB 12 mg intravenously once daily for 3 days, then intramuscularly every other day (approximately ten injections) until discharge. The primary endpoint was the patient's clinical status (7-point Ordinal Scale; OS) on day 15 *versus* that at baseline. The mean duration of hospitalization was 20 days. All patients were alive and discharged with normal oxygen saturation (SpO_2) with no secondary infections or delayed mortality reported by the end-of-study visit (on day 28–72). A decrease in the mean OS and National Early Warning Score values was observed following treatment with AZB. A decrease in OS score was marked in patients identified as severe. Both sets of patients achieved similar

scores, which can be classified as an improvement by day 9–10; SpO_2 levels trended to normalization over time. By day 11–12, all patients had a normal body temperature. Serum C-reactive protein levels decreased in patients with severe and mild disease. Most patients had signs of pneumonia at baseline ($n=27$), with the majority recovering by days 10–12. No major toxicities were observed. AZB was safe and well tolerated when administered in addition to standard of care treatment for COVID-19. Further randomized, placebo-controlled studies are needed to elucidate any potential therapeutic effect in COVID-19.

Keywords: azoximer bromide (Polyoxidonium®), COVID-19, inflammation, interventional study.

Citation

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new virus and the cause of the coronavirus disease (COVID-19) pandemic, causes a spectrum of clinical presentations, ranging from asymptomatic infection to life-threatening illness.¹ More severe disease is characterized by infection of the lower respiratory tract, pneumonia and

respiratory failure, which results in death in about 0.5% of confirmed cases.² In Russia, more than a million cases of SARS-CoV-2 infection have been registered, with more than a million having recovered and more than 23,000 deaths being recorded.³ Although immune therapies and vaccines are becoming available,^{4,5} there still remains no confirmed aetiologic treatments for COVID-19; thus, there is a paramount need to develop a pharmacological defence against COVID-19.

Evidence-based therapy is currently limited to remdesivir, an anti-viral agent that has shown benefits in hospital discharge rates but with some associated toxicity,⁶ and dexamethasone, a broad-spectrum anti-inflammatory providing some relief in patients already requiring respiratory support.⁷

In COVID-19, immune dysregulation is observed in the early stages of the inflammatory immune response, in particular by an increase in inflammasome levels, interferon signaling⁸ and of inflammatory molecules such as IL-6. Innate cells, including neutrophils, myeloid cells, macrophages and natural killer lymphocytes, are key players in the inflammatory immune response. The rapid shedding of the IL-6 receptor (R) during neutrophil pyroptosis augments the IL-6/soluble IL-6R complex (trans-signalling). This enables the targeting of endothelial cells and amplifying the inflammatory process.⁹ The severity of the disease is mainly associated with the rapidity of the constitution of the cytokine storm, with macrophage activation, and myeloid-derived suppressor cells. These are frequently associated with high PD-L1 expression and NETosis, inducing immunothrombosis.^{10,11} In addition, this initial innate deregulated response is followed by an impaired adaptive cell response, with dendritic cell maturation blocked by high levels of IL-6.

The variety of immune disorders offers different targets for therapeutic action on the pathogenic mechanisms of the disease. One of these is IL-6 deregulation, which is associated with immune dysfunction and contributes to the impairment of the immune-mediated virus.¹² The rapid shedding of IL-6R during neutrophil pyroptosis at the very initial phase augments the IL-6/sIL-6R complex (trans-signalling), allowing the targeting of endothelial cells and amplifying the inflammation process.⁹ Dendritic cell maturation is blocked by high levels of IL-6.¹⁰ Unfortunately, anti-IL-6 drugs like tocilizumab and sarilumab do not achieve the desired therapeutic effect in some patients. For example, mortality in the group of patients on non-invasive mechanical ventilation treated with tocilizumab significantly decreased but still amounted to 18%.¹³ Another therapeutic target is myeloid cells.¹⁴ Severe COVID-19 is accompanied by deep immunosuppression with a predominance of immature neutrophils and granulocytic myeloid-derived suppressor cells (up to 90%), which are frequently associated with high PD-L1 expression and NETosis-inducing immunothrombosis and tissue damage.^{11,12}

The reduction of C-reactive protein (CRP) could be a contributing factor, but there is currently no proof to suggest that it is associated with limiting immune suppression, as shown by cytotoxic T cell activity and limiting regulatory T cells *in vitro*. The heterogeneity of clinical manifestations and the complexity of immune disorders in COVID-19 emphasize the need to find new therapeutic solutions with a focus on the mechanisms of cellular modulation. All data indicate the need for immune intervention in COVID-19, particularly with molecules that stimulate both the cellular and humoral response at the same time as reducing the dysregulated inflammatory response.

Azoximer bromide (AZB; Polyoxidonium®) is a high-molecular-weight synthetic immune modulator drug that increases the organism's resistance to local and general infection and is indicated for the treatment of viral infections.¹⁵ *In vitro* studies demonstrated the multiple effects of AZB, including an increase in degranulation of natural killer lymphocytes, an increase of T cell proliferation, and the expansion and maturation of dendritic cells with the expression of several co-stimulatory molecules.¹⁶ AZB penetrates into the cell endosomal segment, where it is associated with increased micromolecular concentrations of hydrogen peroxide, an activator of some signalling molecules and transcription factors, in particular NF- κ B, having detoxifying and antioxidant properties.^{13,17} In clinical use since 1996,¹⁸ AZB has shown a generally well-tolerated safety profile in multiple infectious diseases of viral and bacterial aetiology.^{19,20} The existing non-clinical and clinical data of the action of intravenous and intramuscular AZB provide the rationale to conduct this open-label study to observe its safety profile when added to the complex standard of care (SoC) of patients hospitalized with COVID-19.

The aim of this study was to observe the safety and efficacy of AZB as an addition to the complex treatment of patients hospitalized with COVID-19. This study is the first exploratory use of AZB in patients with COVID-19.

Methods

Study design and participants

This was an open-label, single-arm, multicentre, clinical study in patients with biologically confirmed SARS-CoV-2 infection performed according to the WHO Master Protocol procedures for clinical trials of investigational therapeutics as an adjuvant therapy for the treatment of COVID-19 in hospitalized patients.²¹ The study was conducted at five centres in Russia and one centre in Belarus in accordance with all applicable laws and regulations including, but not limited to, the International Council for Harmonization Guideline for Good Clinical Practice (ICH-GCP), the standards set out by the Research Governance Framework, the Medicines for Human Use (Clinical Trials) Regulations of 2004, and the ethical principles that have their origin in the Declaration of Helsinki. All patients provided either written or verbal informed consent. The trial protocol was reviewed and approved by an Independent Ethical Committee (Pharmnadzor: REC Number 229, April 9, 2020). The trial is registered on ClinicalTrials.gov (NCT04542226).²²

Eligible participants were adults aged 18 years or older, admitted to hospital due to COVID-19 symptoms and with a verified diagnosis of COVID-19 determined by PCR or other commercial or public health assay prior to enrolment. Pregnant or breastfeeding patients, patients with any pathological condition that prevented their participation in the study as judged by the study physician, patients with hypersensitivity and/or intolerance to any ingredient of the investigational

product, or patients with acute or chronic renal failure were excluded (for further details see ref.²²).

Study procedures

All patients screened were included in the study and started dosing on the first day of hospitalization. Demographic data (date of birth, sex and race) and medical history (disease and surgical history, previous (within 4 weeks of the study) and concomitant treatments, medication allergies, tobacco use, alcohol, and/or drugs, as well as the date of onset of COVID-19 symptoms) were collected following signing of the informed consent form. Patients received 12 mg of intravenous AZB (lyophilizate for solution for injections and topical application; NPO Petrovax Pharm) once daily for 3 days (days 0–2), followed by AZB 12 mg administered intramuscularly every other day for 13 days until discharge (days 4–16), in addition to SoC treatment (as described below) for COVID-19 directed by the physician team and according to the recommendations provided by the Ministry of Health of the Russian Federation.²³ The maximum number of injections was ten for patients who were still hospitalized throughout treatment.

Patient clinical status was assessed on days 1, 3, 5, 8, 11, 13 and 15 for the requirement of oxygen, of non-invasive (via mask) or invasive (via endotracheal tube or tracheostomy tube) mechanical ventilation, or of extra corporeal membrane oxygenation. Data were collected following a 7-point Ordinal Scale (OS) as per the WHO Master Protocol (V.3.0, March 3, 2020).²⁴ Further assessments included disease severity based on the 7-parameter National Early Warning Score (NEWS; respiration rate, SpO₂, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness)²⁵ recommended by WHO and multiple organ failure in intensive care patients with septic syndrome using the Sequential Organ Failure Assessment score.²⁶

Other assessments included physical examination (including lung auscultation, data not shown), evaluation of chest X-ray or

CT scans, SpO₂ measurements, electrocardiogram, laboratory tests (haematology, including serum CRP biochemistry and urinalysis), nasopharyngeal and/or oropharyngeal smear collection, and bacteriological inoculation of sputum. Following hospital discharge, patients continued to be monitored until they completed an end-of-study assessment (at least until day 29) conducted in the form of the outpatient visit or by telephone.

Outcome measures

The primary endpoint, as defined in the protocol, was the evaluation of the patient's clinical status using the 7-point OS (Table 1) on day 15, specified as the primary endpoint in the WHO Master Protocol,²⁴ compared with the value at baseline. Secondary outcomes included clinical severity change assessed by the 7-point OS score and NEWS;²⁵ patients' OS and NEWS values on the last observation day (end-of-study assessment); duration of hospitalization (from start until discharge); signs of pneumonia evidenced by CT scans and chest X-rays; body temperature; and blood SpO₂ values (from baseline until day 17). The dynamics and time-to-event analyses were performed for OS score with the threshold set either at 2 or 'discharge from hospital on the next day' whichever occurred first. However, due to specific routine procedures for most patients, discharge occurred earlier than the recording of an OS score of 2. For the over-time dynamics analysis, discharged patients were treated as having an OS score of 2 starting from the next day after discharge until measurement of OS on the follow-up visit. Based on the baseline NEWS values, patients were assigned to one of two groups, namely as having severe (NEWS ≥5, n=22) or mild (NEWS ≤4, n=10) COVID-19.²⁴

Standard evaluation of safety was made, including the cumulative incidence of serious adverse events (AEs) or reactions, the cumulative incidence of AEs or reactions, and the permanent or temporary discontinuation of infusions or injections (by any cause).

Table 1. Seven-point ordinal score according to the World Health Organization Master Protocol.

Ordinal score	Event
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities
3	Hospitalized, not requiring supplemental oxygen
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, on non-invasive ventilation or high-flow oxygen devices
6	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
7	Death

Statistical analysis

We followed a pre-specified statistical analysis plan using intention-to-treat (ITT; all patients who received at least one dose of study drug) analysis as well as informal hypothesis testing (end-of-study *versus* baseline) at the 5% α -level with 95% CIs. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Safety endpoints were described as frequencies (%). Interval (quantitative) data were described using arithmetic mean, standard deviation and 95% CIs for means. Categorical (qualitative) data were described with incidences, percentage or proportions, and 95% CIs for percentage or proportions. The time-to-event data were processed via survival analysis using Kaplan–Meier curves and 95% CIs with no adjustment for potential confounding factors. Standard parametric tests were performed for comparison of quantitative data with normal distribution and included Student's t-test and analysis of variance for repeated measurements. The standard non-parametric Mann–Whitney U, Wilcoxon T and Friedman tests were performed for comparison of quantitative data with distribution other than normal. The Shapiro–Wilk test was used to test the normality of the distribution. Incidences were compared with Pearson's χ^2 test or Fischer's exact test. The significance level was $p=0.05$ (5%) for all statistical analyses.

Results

Patient characteristics and clinical presentation at baseline

Patients were recruited to the study from March 31, 2020 until the 12th of June 2020. A total of 32 patients were included in the ITT population and received AZB. The results are presented for the ITT population. Twelve patients received the complete treatment course of 10 injections of AZB, 11 patients received 9 injections, 8 patients received 8 injections, and 1 patient received 7 injections. Two patients being treated at the same site received 6 mg injections instead of 12 mg. These patients were also receiving treatment for existing cancer and the investigator modified the dose based on their condition and not due to any observed reaction to AZB.

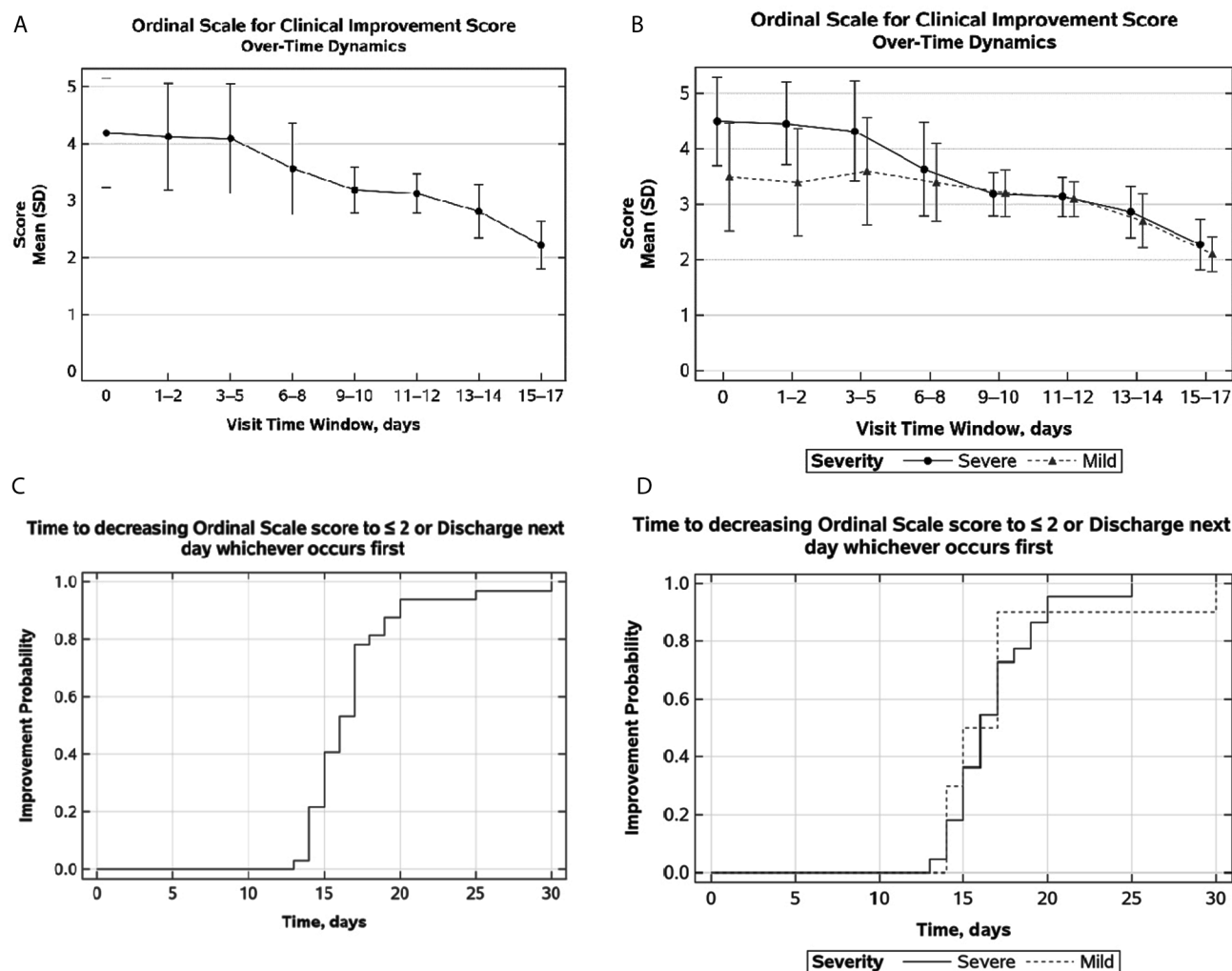
The demographic and baseline characteristics, including comorbidities, severity of disease and duration of symptoms, are presented in Table 2. Patients presented with the following complaints on admission: weakness and fatigue ($n=32$; 100%), cough ($n=29$; 90.6%), dyspnoea ($n=25$; 78.1%), and fever (body temperature $\geq 38^\circ\text{C}$) ($n=22$; 68.8%). Basic anti-COVID-19 medication (SoC) was prescribed according to the existing clinical recommendations²⁷ and included

Table 2. Demographic and baseline characteristics.

Population		Mild disease $n=10$	Severe disease $n=22$
Age, years, mean (SD)	50.59 (11.79)	49.4 (15.6)	51.1 (10.0)
Sex, male/female, n (%)	18 (56.3)/14 (43.8)	4 (40.0)/6 (60.0)	14 (63.6)/8 (36.4)
Ordinal Scale score, mean (SD)	4.19 (0.97)	3.50 (0.97)	4.50 (0.80)
National Early Warning Score values, mean (SD)	6.97 (3.59)	3.00 (1.63)	9.36 (1.71)
Signs of pneumonia, n (%)	27 (84.4%)	6 (60.0)	21 (95.5)
Oxygen saturation (SpO_2), %, mean (SD)	92.23 (3.21)	95.50 (2.01)	90.62 (2.27)
Respiratory support, n (%)			
Invasive lung ventilation	3 (9.4%)	1 (10.0%)	2 (9.1%)
Non-invasive lung ventilation*	9 (28.1%)	0 (0.0%)	9 (40.9%)
Oxygen therapy	11 (34.4%)	2 (20.0%)	9 (40.9%)
None	9 (28.1%)	7 (70.0%)	2 (9.1%)
Time from disease onset to treatment initiation, days	7.55 (4.47)	7.37 (4.65)	7.90 (4.33)
Concomitant medication (by type), n (%)			
Antiretroviral	20 (62.5)	3 (30.0)	17 (77.3)
Anticoagulant	14 (43.8)	4 (40.0)	10 (45.5)
Antimalarial	14 (43.8)	6 (60.0)	8 (36.4)

*Followed by oxygen therapy in some patients.

Figure 1. Evolution of the Ordinal Scale during the azoximer bromide treatment and the follow-up periods: over-time dynamics (panels A and B) and time-to-event analysis (panels C and D) for the whole population ($n=32$) (panels A and C) and the two subpopulations: severe ($n=22$) and mild ($n=10$) COVID-19 (panels B and D).



antiviral therapy, mostly lopinavir plus ritonavir, rarely umifenovir or ribavirin; standard antibiotics, anticoagulants, mostly low-molecular-weight heparin; hydroxychloroquine; and paracetamol and corticosteroids (in two patients). Comorbidities were reported in 19 patients and included arterial hypertension, diabetes, metabolic syndrome, coronary heart disease, chronic kidney disease, arrhythmia, cirrhosis, and cancer. Twenty-seven patients had signs of pneumonia, according to the data obtained from CT scans or X-rays.

Clinical response

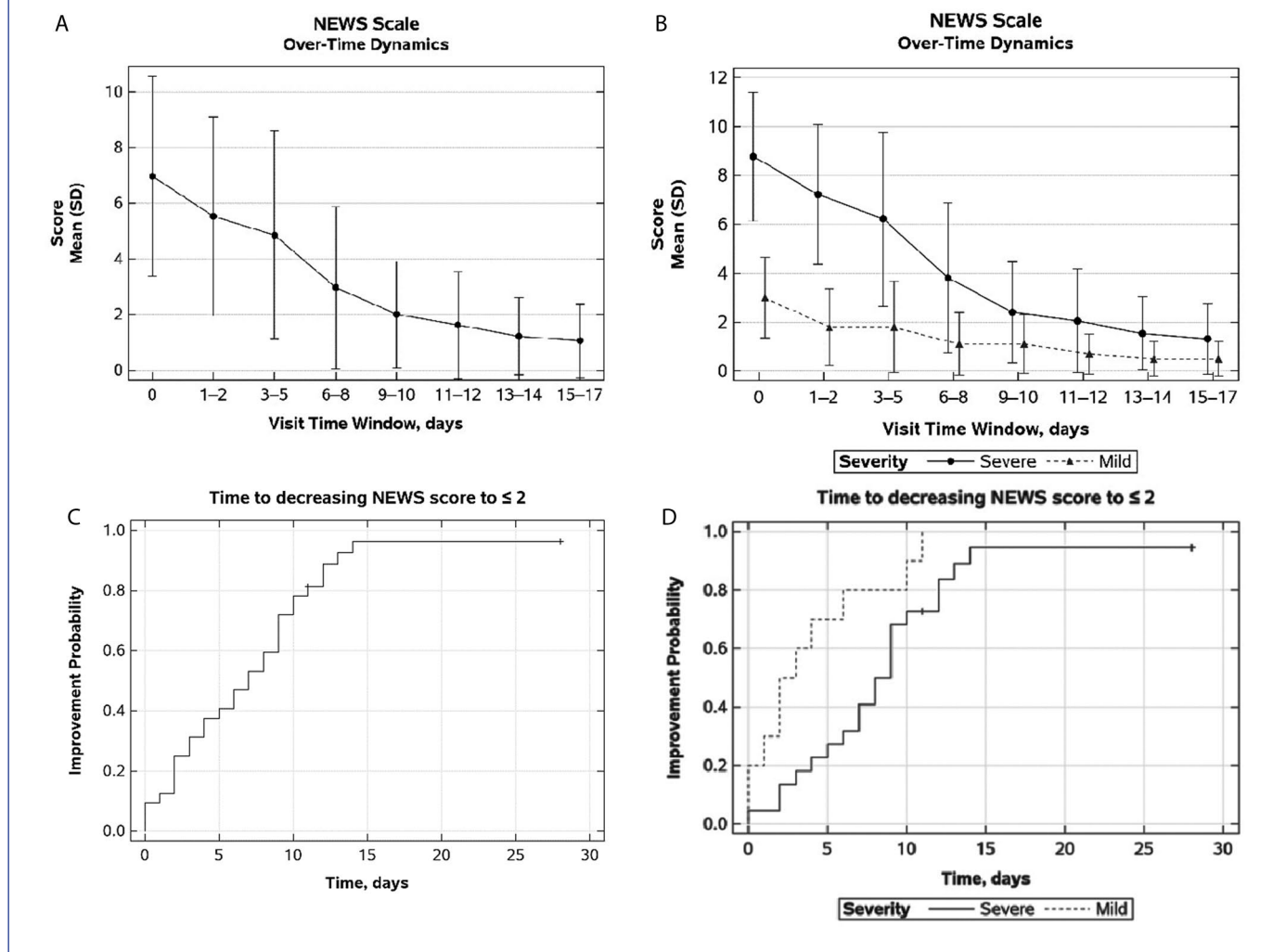
The mean of hospitalization duration was 20.25 ± 4.87 days. The minimal duration of hospitalization was 14 days and maximal duration was 38 days. All patients were alive and discharged from hospital with no secondary infections or

delayed mortality by the end-of-study visit. Discharge from hospital concurred with the OS score reduction from 3 to 2 or 1. The main indicators of pneumonia and lung function (oxygen saturation, pneumonia signs, body temperature) showed gradual recovery and normalization.

A gradual decrease in the mean values of both OS (Figure 1) and NEWS (Figure 2) was observed during the study. The gradual decrease in mean OS score was more prominent in the group of patients with severe disease (Figure 1B). Both groups of patients reached very similar scores, which were classified as an improvement, by days 9–10 (Figure 1B). Patients in the different severity groups had similar rates of discharge.

The dynamics and time-to-event analyses were also performed for NEWS with the threshold set at 2 (Figure 2). Again, the gradual decrease in mean NEWS values was more prominent in

Figure 2. Evolution of National Early Warning Score values during azoximer bromide treatment and the follow-up periods.



the group of patients with severe disease (Figure 2B). Patients in the mild disease group achieved NEWS values ≤ 2 quicker compared with those in the severe disease group (Figure 2B).

Oxygen saturation showed a gradual increase and normalization during the study (Figure 3). All patients were discharged from hospital with normal SpO_2 levels ($\geq 95\%$), including those who had received invasive lung ventilation ($n=3$) or non-invasive lung ventilation ($n=9$), and those with baseline COVID-19 of high severity (NEWS value ≥ 9 , $n=16$). The gradual improvement in blood saturation was more prominent for the severe group (Figure 3B). The increase in blood SpO_2 to normal levels was observed on days 6–8 (Figure 3A). At that point, SpO_2 in the severe disease group approached the corresponding levels observed in the group with mild disease (Figure 3B).

At baseline, 16 (50%) patients had body temperatures of 38°C or above, whereas 6 (18.8%) patients had body temperatures over 39°C . By day 5, the probability of body temperature

normalization was approximately 0.6 (Figure 4). By days 11–12, all patients had a normal body temperature.

C-reactive protein

Mean values in CRP showed a gradual decrease to six times less than those at baseline by day 13 (Figure 5). The decrease in CRP levels was simultaneously observed for both patients with severe and those with non-severe disease.

Pneumonia recovery

In 16 patients, the pneumonia resolved between days 10 and 12 (Figure 6). In 15 patients, all CT scans or X-rays taken during hospital stay showed signs of pneumonia; however, some of these CT or X-rays were taken quite early and no further CT or X-ray evidence was available for these patients. A standard improvement probability curve was plotted for the whole population, including those 15 patients who

Figure 3. Improvement of SpO₂ during azoximer bromide treatment: in the overall population (panel A, *n*=32) and in patients with severe (*n*=22) and mild (*n*=10) COVID-19 (panel B).

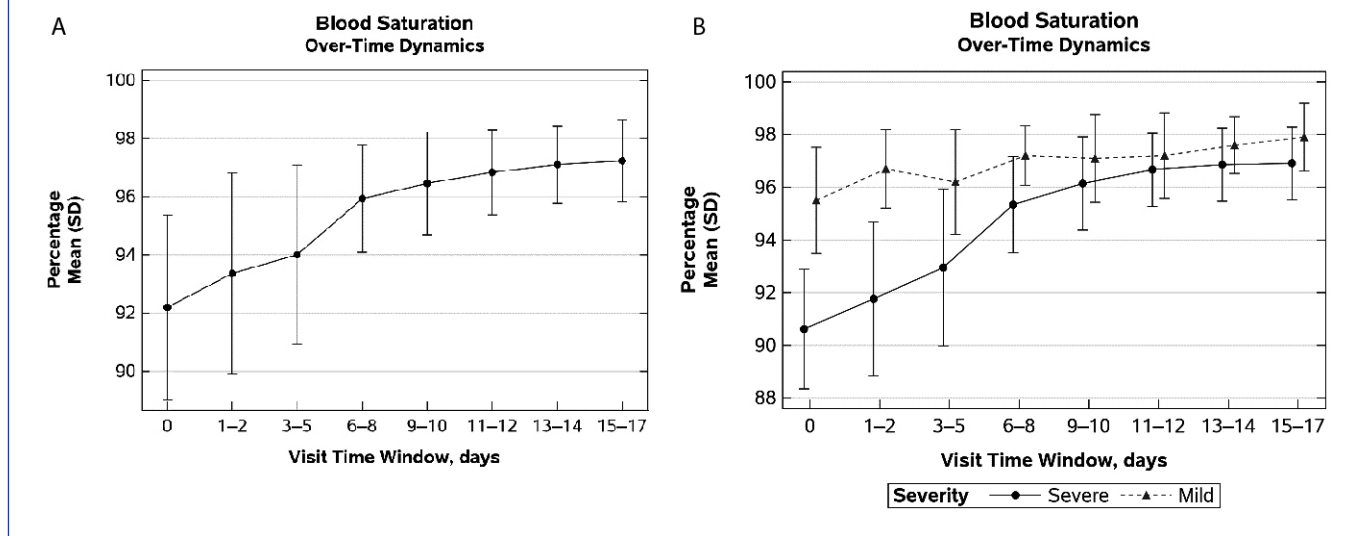


Figure 4. Time-to-event analysis of the evolution of body temperature during treatment with azoximer bromide and the follow-up period in the overall population (*n*=32).

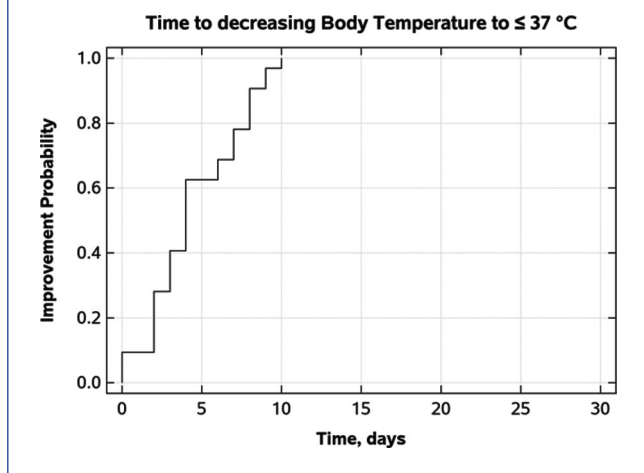
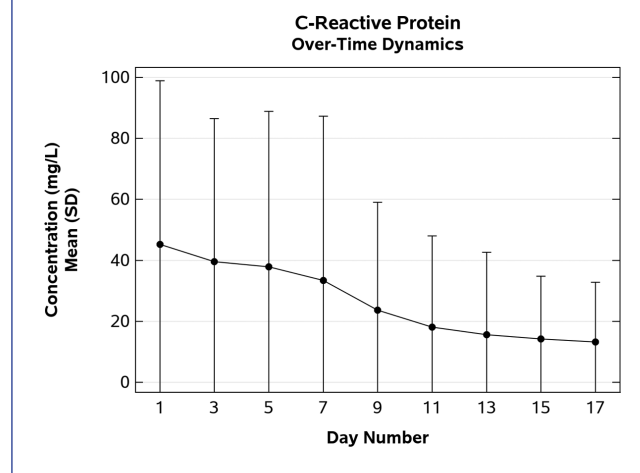


Figure 5. C-reactive protein dynamics.



retained some pneumonia signs by CT or X-ray investigation (Figure 6).

Concomitant medications

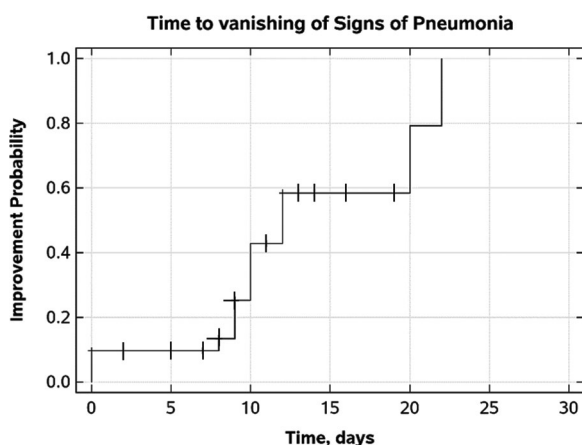
A comparison of the gradual changes in NEWS values, OS score, blood SpO₂ and body temperature was performed in subgroups of patients defined by concomitant medications. There were three such subgroups: antivirals, anticoagulants and hydroxychloroquine (Table 2). However, no essential differences were observed for these parameters in these patient subgroups. The only remarkable finding was the difference in baseline

severity of symptoms between patients who did or did not receive antiviral medication: NEWS values were substantially higher in patients receiving antiviral therapy at baseline. In the anticoagulant subgroup, the NEWS values for patients treated and untreated were similar at baseline. NEWS values for patients who received hydroxychloroquine at baseline were lower than for those who did not receive treatment.

Safety

No major toxicities were observed during this study. Four AEs were recorded in four patients, including prolongation

Figure 6. Time-to-event analysis of pneumonia symptoms dynamics during treatment and follow-up periods.^a



^aObservations from patients who retained pneumonia signs ($n=15$) were denoted by crosses, disappearance of pneumonia in patients with improvement, evidenced by computed tomography scan and X-ray ($n=16$), was shown by steps.

of the pulse rate interval on the electrocardiogram, possibly associated with the lopinavir plus ritonavir treatment in two patients and with hyperthermia, considered by the investigator as a reason to postpone the next AZB injection for 1 day; no association with AZB therapy was established in two patients. All AEs were not serious they resolved without additional interventions or by AZB therapy cessation. All four AEs were not associated with AZB treatment but were rather consequences of other therapies or of severe COVID-19. It is worth mentioning that all four patients who developed AEs had maximum NEWS values of 9–13.

Discussion

At the time of writing, Russia ranks fourth place in terms of the number of detected cases of COVID-19 worldwide. More than 1.2 million cases of infection have already been noted; it is most likely that the COVID-19 epidemic will continue both in Russia and the world for the foreseeable future. Russian epidemiologists predict that SARS-CoV-2 may become a constantly circulating virus and, together with other respiratory viruses (influenza viruses, rhinoviruses, etc.), will cause new outbreaks of the disease in all parts of the world. In many countries, the active development of vaccines against COVID-19 is underway and they are gradually being implemented.

AZB represents a class of drugs that could be termed 'regulators of inflammation/immunity'. AZB has been shown to reduce the inflammatory process in patients

with COVID-19, including in those with severe disease as well as in patients with dysimmune diseases or other infections, due to its early anti-oxidant, pro-phagocytosis and anti-inflammatory properties.^{13,15,28,29} In addition, AZB has been shown to stimulate the immune response by promoting antigen presentation and cytotoxic activity.¹⁶ In the present study, AZB was safe and well tolerated and showed promising results in decreasing the OS and NEWS values, decreasing CRP (an infection marker), increasing blood saturation and decreasing body temperature; these effects were observed even in patients with severe COVID-19 (NEWS ≥ 5).

No deaths were observed in the study population receiving AZB. Considering the rates of mortality reported for similar populations of patients with COVID-19 in Russia at the time of this study,³⁰ estimates suggest that, with 23 patients admitted needing respiratory support, we should have expected at least five deaths in the study population. Furthermore, there was a relatively high incidence of comorbidity in our patient group (19/32 patients had co-morbidities including diabetes and other types of 'weighted' co-morbidities). As patients with comorbidities tend to experience less fortuitous outcomes following COVID-19,³¹ the absence of mortality in our study group appears to support a beneficial effect of AZB that warrants further investigation in an adequately controlled, randomized clinical trial.

The decrease in OS score from baseline to days 15–17 was less prominent than the NEWS values and was not sufficient to evaluate the patients' clinical improvement. Time-to-event analysis also showed that, according to the OS score, the turning time point for improvement was shifted rightwards along the time axis (i.e. it occurred later) compared with the same analysis of the NEWS values. Thus, most patients reached the NEWS value of 2 faster than they were discharged from hospital. Thus, in the current study, with the given threshold values, the NEWS scale is likely to have been more sensitive to changes in patients' condition and to better reflect the overall recovery process.

AZB was administered in addition to SoC treatments such as antiviral medication, anticoagulants or hydroxychloroquine and no apparent interaction with any of these drugs was noted, further confirming its safety and tolerability. There were differences in symptom severity at baseline between patients with regard to their treatment: NEWS values for patients who received hydroxychloroquine at baseline were lower than those of patients who did not receive this treatment. These differences could represent the real therapeutic situation presently available, which varies greatly from site to site and from country to country as well as according to physicians' personal clinical judgement.

The limitations of the present study include the fact that it was conducted as an open-label, multicentre, non-interventional observational study in the absence of a

formal control group. Patients received various treatment regimens for COVID-19 (antiviral agents, antimalarial agents, anticoagulants, etc.), depending on local management protocols. Consequently, it is not possible to fully identify the exact impact, if any, of AZB on the patient outcomes. However, we feel that the present data provide a signal of possible beneficial effects in the absence of safety concerns that should be investigated in appropriately powered and designed clinical trials.

Conclusion

In conclusion, this preliminary study shows that AZB at 12 mg intravenously once daily for 3 days, then intramuscularly every other day until discharge, can be administered safely in hospitalized patients with COVID-19. Based on these results, a randomized multicentre, double-blind, placebo-controlled comparative clinical trial in hospitalized patients with COVID-19 has been set up and is currently under way.³¹

Trial registration: The trial is registered on ClinicalTrials.gov (NCT04542226).

Contributions: All authors contributed equally to the preparation of this review. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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