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Anti-Lethal Therapy of COVID-19 for Home Health Outpatient Therapy

Oleg Bukhtoyarov and Denis Samarin

ABSTRACT

The article presents the rationale for a new therapeutic strategy for treatment of patients with COVID-19, based on the combined use of biologic response modifiers and drugs targeting etiology and pathophysiology of the novel coronavirus infection, excluding disadvantages of polypharmacy, and providing a high clinical effect. This approach has been predominantly used in home health outpatient treatment of 324 patients with COVID-19 of variable severity using the biologic response modifiers "double drug cocktail" made of recombinant human interleukin-2 and recombinant human interferon alpha-2b in combination with alimemazine, nimesulide, rivaroxaban and antibiotic therapy (co-amoxiclav, or ceftriaxone) if secondary bacterial pneumonia was diagnosed. The results obtained indicate a dramatic improvement in the condition of patients, even with a severe COVID-19, which made possible to avoid artificial ventilation and prevent deaths.

Keywords: Anti-lethal therapy, COVID-19, Cytokines, Interleukin-2, Interferon alpha-2b, Outpatient treatment.

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Dr. Oleg Bukhtoyarov*
Medical Center 39 Ltd, Kaliningrad, Russian Federation.
(e-mail: bukhtoyarov@mail.ru)
Dr. Denis Samarin
Laboratory of Psychoimmunology, Medical Center 39 Ltd, Kaliningrad, Russian Federation.
(e-mail: d.m.samarin@ngs.ru)

****Corresponding Author***

I. Introduction

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) led to occurrence of 181 521 067 COVID-19 cases and 3 937 437 global deaths as of 30 June 2021 [1]. COVID-19 pandemic caught by surprise healthcare systems of all countries around the globe. Due to lack of scientific evidence, it especially appeared in the empirical approach to the treatment of patients with COVID-19 polypharmacy, and in the constant change of potential drug candidates for COVID-19 therapy. Some drugs were not effective enough, like azithromycin [2], while others (for example, heparin, chloroquine, etc.) turned out to be unsafe for patients because they had numerous side effects in the hematopoietic and cardiovascular systems [3]. Treatment of COVID-19 patients with underlying chronic diseases (diabetes mellitus, cardiovascular diseases, etc.) presents significant difficulties [4].

The outcome of COVID-19 in each individual patient depends on the predominance of the mechanisms of etiopathogenesis (the onset and development of the disease) and sanogenesis (self-healing of the body) [5]. These mechanisms are closely related, but opposite in their biological orientation. It is logical to argue that a high therapeutic effect can be achieved with an etiopathogenetically and sanogenetically oriented approach to handling patients with COVID-19. In this regard, the following etiopathogenetic mechanisms of COVID-19 are of particular importance for the development of therapeutic strategies: direct viral toxicity, endotheliopathy, hypercoagulability, vasculitis, immune system dysregulation with non-specific hyperinflammatory state (cytokine storm), maladaptation of the angiotensin-converting enzyme-2 (ACE2) pathway [6], [7].

A terrible complication of severe COVID-19 is acute respiratory distress syndrome with multiple organ failure [8]. The impossibility of quick discovery and production of new drugs for the treatment of COVID-19 has led to a revision of indications for already known drugs in the treatment of other diseases, thereby realizing a drug repurposing strategy [9], [10]. This strategy has resulted in dozens of candidate drugs for the treatment of COVID-19 from various pharmacological groups [11], [12]. In our opinion, all candidate drugs from this large list are exclusively etiopathogenetically and symptomatically oriented with "anti-" effects, but there are no drugs with biologic response modifiers effects, i.e., with natural sanogenetic "self-repair" effects in it. The US National Institutes of Health (NIH) presented, in our opinion, a number of drugs for sanogenetic therapy of COVID-19 from the group of biologic response modifiers: interferons (IFN alfa-2b, IFN beta-1a, IFN beta-1b) and non-SARS-CoV-2 specific immunoglobulin [13].

Currently, we observe that the long-forgotten sanogenetic therapy is reviving under the name of Low-dose medicine (LDM) [14].LDM is based on the use of fundamental biologically active molecules (cytokines, neuropeptides, hormones, growth factors), which are usually present in the body of a healthy person and regulate cellular and tissue metabolism. It should be noted, that the LDM treatment of COVID-19 also received theoretical justification [15].

We used two immunotherapeutic drugs in the sanogenetic therapy of COVID-19: recombinant human interleukin-2 (rhuIL-2) – Roncoleukin® (approved by order No. 249 of Ministry of Health, Russian Federation, August 31, 1995, Registration Certificate No. LS-001810, Research and Production Company BIOTECH, Ltd) and recombinant

human interferon alpha-2b (rhIFNα-2b) – Viferon® (approved by order No. 192 of Ministry of Health, Russian Federation, September 27, 1994, Registration Certificate No. 96/432/5, Pharmaceutical Company FERON, Ltd). The clinical results of our proposed therapeutic approach in the treatment of patients with COVID-19 mainly on an outpatient basis are presented in this work.

A. Search Strategy and Selection Criteria

We searched for scientific articles published before April 05, 2021, without language restrictions using the search engines Google, Google Scholar and electronic research databases PubMed / Medline, SCOPUS, Web of Science. Our search strategy used combinations of keywords including "SARS-CoV-2", "COVID-19", "Pathogenesis", "Inflammation", "IL-2", "IFNα-2b", "Alimemazine", "Nimesulide", "Rivaroxaban", "Autonomic dysfunction", "Outpatient", "Treatment", "Neuro-COVID". We also reviewed papers prepared by the World Health Organization (WHO) and NIH (USA). Articles published primarily in 2020 and 2021 were included.

II. New Strategy for Home Health Outpatient Therapy of COVID-19: our Results

A. Patients

From May 11, 2020 to February 07, 2021, 324 patients (166 women and 158 men) aged 6–84 years with a confirmed diagnosis of COVID-19 (PCR detection of SARS-CoV-2 RNA in respiratory samples) were treated in accordance with our recommendations in the following regions: Germany (Trossingen) – four; Italy (Bellamonte – three, Moena – three); Kazakhstan (Baikonur) – 20; Republic of Belarus (Rechytsa) – five; Russian Federation (Moscow – 52, St. Petersburg – 21, Kaliningrad – 138, Kemerovo – five, Nizhny Novgorod – 15, Omsk – six, Orenburg – eight, Samara – 32, Stavropol – six); Switzerland (Sankt Gallen) – three; USA (Brooklyn Center, MN) – three.

319 patients received home health outpatient therapy of COVID-19: mild COVID-19 – 202 patients (without evidence of viral pneumonia or hypoxia, fever < 37.8 °C), moderate COVID-19 – 104 patients (75 patients with clinical symptoms of viral pneumonia: fever > 38 °C, chills, respiratory rate > 22 breaths / min, dyspnoea, nonproductive cough, rhinitis, myalgias, headaches, fatigue, but no signs of severe pneumonia; 29 patients with clinical symptoms of bacterial pneumonia: cough with mucus that is yellow, green, or tinged with blood, stitching chest pain in the that is worse when coughing or breathing and rigors), severe COVID-19 – 13 patients (clinical signs of bacterial pneumonia, respiratory rate > 30 breaths / min, volume lung lesions 55-72% according to computed tomography, blood saturation level (SpO_2) 90-75%). All patients with severe COVID-19 were from Russia (Nizhny Novgorod – five, Kaliningrad – four, Samara – three, St. Petersburg – one). Five patients out of all these patients were treated in the intensive care unit.

Treatment of patients with moderate and severe COVID-19 on an outpatient basis (at home) quite unexpectedly turned out to be a necessary measure. Practically, all patients and / or their relatives firmly refused hospitalization "for fear of dying in the hospital", as they witnessed deaths in the hospital among their relatives, acquaintances and friends. They sought help from Medical Center 39 Ltd (Kaliningrad), because they had information about the successful outpatient treatment of COVID-19. We accompanied the outpatient treatment of patients with remote consultations, except for seriously ill patients in Kaliningrad, who were provided with in-person outpatient care. We realized the full responsibility of the outpatient treatment of COVID-19 and warned patients about immediate inpatient treatment in case of the slightest deterioration in their condition. The first patient with successful outpatient home treatment according to our proposed protocol of moderate COVID-19 (Table I) was the wife of one of the authors of this article.

B. Sanogenetic Regulatory Cytokine IL-2: Rationale for Use in Patients with COVID-19

Interleukin-2 (IL-2) plays a key role in the regulation of specific immunological processes and is a vital, proliferative factor for lymphocytes, which retain their viability only when it is present [16]. A deficiency of IL-2 occurs in COVID-19 patients along with the death of a significant number of lymphocytes (T cells) [17], what leads to obstruction of specific immune responses, generalization of the infectious process and inflammation. In addition, with COVID-19, clones of lymphocytes responsible for tissue repair tend to survive, which is correlates with a high risk of autoimmune diseases development [18].

IL-2 plays a decisive role in the expansion of regulatory T cells (Tregs) that help establish a balance between defense against pathogens and avoidance of autoimmune disease [19].IL-2 deficiency leads to a decrease in Tregs and the development of fatal inflammatory and autoimmune diseases that can be suppressed by restoring the normal number of Tregs [20]. By the way, the number of Tregs inversely correlates with the severity of COVID-19 [21]. It is important to know that Tregs are 7-10 times more sensitive to IL-2 than natural killer (NK cells), therefore a "low dose" of IL-2 in the range of 1-3 x 10^6 IU / m^2 body surface area / day reliably increases Tregs, but also increases the number of NK cells. If we reduce IL-2 to "ultra-low dose", i.e., 10 to 50 times, Tregs expansion continues, but with much less effect on NK cells [22]. Low doses of IL-2 selectively activate Tregs through an IL-2-dependent transcriptional amplification mechanism, which provides the molecular basis for low and ultra-low dose IL-2 therapy to achieve powerful anti-inflammatory effects and immune tolerance [23].

There is sufficient theoretical justification for the use of IL-2 in the treatment of COVID-19 [24] and encouraging results have been obtained from the use of rhuIL-2 in addition to regular treatment of severe COVID-19 [25]. We used an ultra – low-dose of rhuIL-2 (Roncoleukin®) 5×10^5 IU for in home health outpatient therapy of COVID-19 (Table I). We deliberately used ultra-low-dose of rhuIL-2 (Roncoleukin®) to avoid the risk of increased biological effector pro-inflammatory functions of CD4 T cells, CD8 T cells and NK cells [26], which could exacerbate the disease and increase autoimmunity.

C. Sanogenetic Antiviral Cytokine IFNα-2b: Rationale for Use in Patients with COVID-19

Type I interferons (IFNs), including IFNα-2b, are key elements of the immune response, the first line of defense of

the immune system against infectious agents and tumor progression. A sufficient amount of interferons in the body leads to an accelerated maturation of cells of the immune system with a complete development of their protective functions, acting synergistically with IL-2 [27], [28]. However, SARS-CoV-2 inhibits the production of endogenous interferons with the rapid development of infection, the appearance of severe pulmonary and multi-organ lesions in COVID-19 [29]. IFNs deficiency, in particular IFNα, is a distinctive feature of coronavirus infection, which is accompanied by a high viral load and a more severe course of COVID-19 [30], [31]. Moreover, IFNs production deteriorates significantly with age [32], which could be critical for elderly COVID-19 patients. At the same time, SARS-CoV-2 is highly sensitive to exogenously added interferons, in particular to rhIFNα-2b [33].IFNs dose-dependently inhibit the replication of the SARS-CoV-2 virus that making them good candidates for the management of COVID-19 [34].

IFNα-2b is included in the WHO's list of essential medicines and is used for antiviral and anticancer therapy [35]. IFNα-2b stimulates the expression of the ACE2 receptor in epithelial cells of the human nose and the SARS-CoV-2 virus binds precisely to the inactivated ACE2 receptor. Therefore, by increasing the expression of ACE2 receptors and translating them into an activated state, IFNα-2b increases tolerance to SARS-CoV-2 [36]. IFNα-2b therapy shortens the duration of SARS-CoV-2 release, reduces the level of markers of acute inflammation [37], prevents the severe course of COVID-19 [38] and reduces mortality in COVID-19 patients [39].

In our outpatient treatment protocols, we aimed to use rhIFNα-2b (Viferon®) as rectal suppositories as early as possible at a dosage of 3×10^6 IU once or twice a day, depending on the severity of COVID-19 (Table I), in order to prevent more severe course of COVID-19.

D. Justification of the Need for Timely Treatment of Hypersympathicotonia in Patients with COVID-19

The widely presented symptomatology is so called "neuro-COVID" [40], i.e. the neurological, psychiatric and psychological manifestations related to COVID-19, is due not only to psychogenic factors, but also neuroinflammation caused by direct and indirect neurotoxicity of SARS-CoV-2, high levels of pro-inflammatory cytokines IL-6, TNF-α, IL-1β in plasma, cerebrospinal fluid, brain of patients [41], [42]. As well as over-excitation of the sympathetic nervous system through its main neurotransmitter norepinephrine (also called noradrenaline) [43], which in turn leads to direct suppression of the antibacterial functions of neutrophils, forming higher susceptibility of patients to infectious complications [44].

Excessive sympathicotonia is a common pathophysiological feature in patients with hypertension, heart disease, diabetes and other diseases which present as comorbidities in COVID-19 patients, have a higher risk of developing life-threatening complications [45], including, for example, stress-induced cardiomyopathy – Takotsubo Syndrome [46]. Earlier, in experimental psychoneuroimmunological studies in oncology, it was convincingly shown that induced hypersympathicotonia led to a 30-fold increase in metastases to distant tissues [47]. Thus, extreme sympathicotonia is a powerful factor in immunosuppression and generalization of the inflammatory process in patients with COVID-19, as well as an important target for therapeutic intervention.

For the relief of nosogenic reactions and excessive sympathicotonia in patients with COVID-19 (except for children), we used the antipsychotic medication alimemazine/trimeprazine (Teralidgen®), which in a dosage of 5 mg 1, or 2 times a day proved to be an effective drug capable sufficiently and quickly discontinue anxiety-phobic symptoms and autonomic reactions in patients with COVID-19, associated, for instance, with hypertension, hypotension, tachycardia, which were resistant to appropriate drug therapy. In addition, Teralidgen® showed a clinically balanced somnolent, sedative and antihistamine effect. Furthermore, in the experiment trimeprazine proved to be a promising inhibitor, of SARS-CoV-2 by blocking the viral penetration stage [48].

E. Other Components of COVID-19 Anti-Lethal Outpatient Therapy

We chose Rivaroxaban (Xarelto®) at a dosage of 10 mg once a day for the prevention of blood clots formation of the entire severity of COVID-19, because there was no need for the blood clotting control. Additionally, anticoagulant and antiplatelet therapy goes along with an anti-inflammatory effect [49].

In our clinical practice, we were convinced of the safety and efficiency of non-steroidal anti-inflammatory drugs nimesulide (Nise®) with prolonged use (about a year), so we confidently used it in the COVID-19 treatment protocols. It is known that nimesulide abolishes the transport function of a broad spectrum of neutral (0) amino acid transporter B0AT1 (encoded by the SLC6A19 gene), which stabilizes the dimeric receptor ACE2-B0AT1, which is targeted by SARS-CoV-2 [50]. Thus, nimesulide probably also has an indirect antiviral activity.

Antibiotic therapy was used in 28% of patients with moderate COVID-19 (co-amoxiclav) only with clinical signs of secondary bacterial pneumonia and in all patients with severe COVID-19 (ceftriaxone) in whom bacterial coinfection is a high risk factor for mortality [51]. It is noteworthy that none of the diagnostic indicators such as procalcitonin and C-reactive protein has significant additional value in patients with COVID-19 for bacterial co-infection diagnosis comparing to clinical criteria [52].

F. Clinical Effects and Treatment Outcomes

The results of sanogenetic cytokine therapy with rhuIL-2, and rhIFNα-2b in complex outpatient home treatment of patients with COVID-19 of varying severity turned out to be more than positive.

TABLE I: THE SCHEME OF HOME HEALTH OUTPATIENT THERAPY OF COVID-19 AND POST-ACUTE COVID-19 SYNDROME

	Group	Drugs	Trademark	Mechanism of action	Dosing
Mild COVID-19					
	Immunomodulators	Recombinant human interleukin-2 (from recombinant strain of non-pathogenic brewer's yeast Saccharomyces cerevisiae) (Solution in ampoules)	Roncoleukin®	Vital growth and differentiation factor for antigen-activated T-, B-lymphocytes, and NK cells; critical survival / growth factor for FOXP3 + regulatory T cells; increases the production of IFN-gamma, etc.; prevents apoptosis of activated T-lymphocytes; increases the synthesis of IgM, IgG, IgA by plasma cells; activates the processes of tissue repair and regeneration; suppresses autoimmunity in low-dose.	Day 1–6: 5×10^5 IU / every other day, subcutaneously.
	Immunomodulators	Recombinant human interferon alpha-2b with antioxidants (ascorbic acid, and α-tocopherol acetate) (Rectal suppositories)	Viferon®	Binds to type-1 interferon receptors, leading to the dimerization of JAK1 and JAK2 receptors, that leads to JAK trans-phosphorylation, and phosphorylation of STAT1 and STAT2. Dimerized STAT activates multiple antiviral proteins. Inhibits viral replication, viral proteases, increases phagocytic activity of the macrophages, and the specific cytotoxicity of lymphocytes. Accelerates the maturation of cells of the immune system, normalizes the antioxidant status and protease activity of blood plasma, enhancing antiviral and antiproliferative activity 10-14 times.	Day 1–10: 3×10^6 IU / daily bedtime, per rectum.
	Direct oral anticoagulant, factor Xa inhibitor	Rivaroxaban (Tablets)	Xarelto®	Direct, specific inhibition of endogenous factor Xa activity, potently inhibition prothrombinase activity, inhibition of thrombin generation and amplification processes of coagulation, increasing the permeability and degradability of the whole blood clot by reducing the formation of thrombin.	Day 1–10: 10 mg / once a day, orally.
	Non-steroidal anti-inflammatory drugs	Nimesulide (Tablets)	Nise®	Inhibition of cyclooxygenase COX-2, phosphodiesterase type 4, proteases (elastase, proteinase), histamine release from human basophil, and mast cells; inhibition of histamine activity, and the synthesis, release of the substance P; reduced generation of superoxide anion O2; scavenging of hypochlorous acid; activation of glucocorticoid receptor system.	Day 1–10: 100 mg / once a day, orally.
	Neuroleptics	Alimemazine tartrat (Tablets)	Teraligen®	Blockade of dopamine D2 receptors of the mesolimbic, and mesocortical systems (antipsychotic effect), blockade of D2 receptors in the trigger zone of the vomiting center (antiemetic effect), blockade of adrenergic receptors of the reticular formation of the brain stem (sedation effect), blockade of dopamine receptors of the hypothalamus (hypothermic effect), blockade of agonist action of histamine at the H1 receptor (antihistamine effect), reducing the activity of the NF-κB immune response transcription factor through the phospholipase C, and the phosphatidylinositol (PIP2) signalling pathways decreases antigen presentation and the expression of pro-inflammatory cytokines, cell adhesion molecules, and chemotactic factors (anti-inflammatory effect).	Day 1–10: 2.5 or 5 mg / at night, orally.
Moderate COVID-19					
	Immunomodulators	Recombinant human interleukin-2	Roncoleukin®	See above	Day 1–12: 5×10^5 IU / every other day, subcutaneously.
	Immunomodulators	Recombinant human interferon alpha-2b	Viferon®	See above	Day 1–14: 3×10^6 IU / twice a day, per rectum.
	Non-steroidal anti-inflammatory drugs	Nimesulide	Nise®	See above	Day 1–14: 100 mg / twice a day, orally.
	Direct oral anticoagulant, factor Xa inhibitor	Rivaroxaban	Xarelto®	See above	Day 1–14: 10 mg / once a day, orally.
	Neuroleptics	Alimemazine tartrat	Teraligen®	See above	Day 1–14: 5 mg / at night, orally.
Presence of clinical symptoms of bacterial infection	Antibiotic, semisynthetic penicillin and β-lactamase inhibitor	Amoxicillin+clavulanic acid (Co-amoxiclav) (Tablets)	Amoxiclav®	Amoxicillin binds to the penicillin-binding protein enzyme and inhibits peptidoglycan synthesis by destroying the cell wall and lysis of the bacteria. Clavulanic acid inhibits and deactivating the beta-lactamases, thus blocking hydrolyze the beta-lactam ring restoring the antimicrobial effects of amoxicillin.	Day 1–5 (or 7): 875 mg + 125 mg / twice a day, orally.

	Group	Drugs	Trademark	Mechanism of action	Dosing
	Drugs normalizing of intestinal microflora, in combinations	Bifidobacterium longum Enterococcus faecium (Capsules)	Bifiform®	Probiotic activity provided by strains of bacteria with a predictable high level of antibiotic resistance, which actively colonize small, large intestine, and produce acetic, lactic acid, thereby inhibiting the growth, and reproduction of pathogenic microorganisms.	Day 1–14: one capsule / three times a day, orally.
Sever COVID-19					
	Immunomodulators	Recombinant human interleukin-2	Roncoleukin®	See above	Day 1–18: 5×10^5 IU / every other day, subcutaneously.
	Immunomodulators	Recombinant human interferon alpha-2b	Viferon®	See above	Day 1–20: 3×10^6 IU/ twice a day, per rectum.
	Non-steroidal anti-inflammatory drugs	Nimesulide	Nise®	See above	Day 1–14: 100 mg / twice a day, orally.
	Direct oral anticoagulant, factor Xa inhibitor	Rivaroxaban	Xarelto®	See above	Day 1–20: 10 mg / once a day, orally.
	Neuroleptics	Alimemazine tartrat	Teraligen®	See above	Day 1–20: 5 mg / twice a day, orally.
Presence of clinical symptoms of bacterial pneumonia	Third-generation cephalosporin antibiotic	Ceftriaxone (Powder vials for injection)		Binds, inactivates penicillin-binding proteins, and interferes with the cross-linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity. This results in the weakening of the bacterial cell wall and causes cell lysis.	Day 1–7 (or 10): 2 g vial with 0.9% Sodium chloride injection 100 mL / once a day, intravenously.
	Drugs normalizing of intestinal microflora, in combinations	Bifidobacterium longum Enterococcus faecium	Bifiform®	See above	Day 1–14 (or 17): two capsules / twice a day, orally.
Post-acute COVID-19 syndrome (Long covid)					
	Immunomodulators	Recombinant human interleukin-2	Roncoleukin®	See above	Day 1–60: 2.5×10^5 IU / every other day, subcutaneously.
	Immunomodulators	Recombinant human interferon alpha-2b	Viferon®	See above	Day 1–30: 3×10^6 IU / daily bedtime, per rectum.
	Non-steroidal anti-inflammatory drugs	Nimesulide	Nise®	See above	Day 1–14: 100 mg / twice a day, orally.
	Neuroleptics	Alimemazine tartrat	Teraligen®	See above	Day 1–30: 5 mg / once or twice a day, orally.

With the beginning of therapy, not a single patient experienced a deterioration in health, there was no indications for artificial ventilation, and no single death, all patients recovered. Generally, hyperthermia disappeared on a second or third day with a remarkable clinical improvement in well-being in the following days and the reestablishment of the normal level of oxygen saturation. The complex therapy of patients with COVID-19 did not require the prescription of dexamethasone since the patients' well-being was steadily improving. Such a noticeable improvement in the well-being of patients has always been observed, including elderly patients with associated chronic diseases. Several children fell ill with mild COVID-19 along with their mothers; and all children were prescribed only rhIFNα-2b at a dosage of 1×10^6 IU at night from the first day of illness. Within 7 days, all children completely recovered from COVID-19 and their well-being was returned.

We have obtained many clinical observations indicating the effectiveness of the proposed therapeutic approach. For example, a 54-year-old man (from Kaliningrad), a doctor with COVID-19 developed secondary cerebral vasculitis (sudden neurological deficit – paresis of the left foot, and neuropathy of the lateral cutaneous nerve of the left thigh; reduced visual acuity; diffuse headache; cognitive and affective disorders), and inflammatory cardiomyopathy, i.e. myocarditis (increase in the size of all the chambers of the heart, atrial extrasystoles with numerous episodes of allorhythmia (bi-, tri-, quadrigeminia). His signs of cerebral vasculitis, and myocarditis were completely stopped with the restoration of the normal size of the heart, heart rate, and well-being. With use of sanogenetic cytokine therapy rhuIL-2 (2.5×10^5 IU / every other day, 30 subcutaneous injections), and rhIFNα-2b (3×10^6 IU morning and night, 20 days) and alimemazine (5 mg daily at night, 30 days), and nimesulide (100 mg twice a day for 20 days)

Two cases were clinical findings: significant regression of the parkinsonism syndrome, patients suffered for many years with the restoration of the ability to write and independently intake food was observed during treatment with rhuIL-2, and rhIFNα-2b in an 82-year-old woman (from Samara), and a 74-year-old man (from Kaliningrad), in addition to the complete relief of moderate COVID-19 symptoms. The clinical effect was detected for three weeks, followed by the return of the previous symptoms of parkinsonism.

The effective use of sanogenetic cytokine therapy in the treatment of COVID-19 was the basis for using this approach in the treatment of the so-called "Post-acute COVID-19 syndrome" (PACS), or "Long covid", the alleged pathogenesis of which is associated with direct infection with SARS-CoV-2, inflammation, autoimmune response, hypercoagulability, metabolic or hypoxic damage [53], [54], as well as in our opinion, a pathological state of the immune system referred to as homeostatic proliferation [55]. Almost all patients who came to us with PACS symptoms have received prior COVID-19 treatment in other medical institutions. PACS symptoms appeared 10–14 weeks after the onset of the disease, were very persistent and heterogeneous: hyposmia/dysgeusia, cognitive disturbances, anxiety, fatigue, arterial hypertension, etc.

A feature of our proposed PACS therapy was the half dosage of rhuIL-2, and rhIFNα-2b (compared to dosages in the treatment of COVID-19) and a longer duration of therapy (from 20 to 60 days) in combination with appropriate symptomatic, and pathogenetic treatment PACS (table 1), in fact, has proven to be more resistant to therapy than COVID-19 itself. Among the patients whom we previously treated with COVID-19, only seven people (2.2%) presented with PACS symptoms.

III. Conclusion

Despite the emergence of different COVID-19 vaccines, the race for therapies for COVID-19 is steadily accelerating [56], but efficacy and safety should be paramount in treatment protocols. Our clinical experience has shown that the sanogenetic cytokine "double drug cocktail" of rhuIL-2, and rhIFNα-2b is an important and safe clinical add-on into any treatment protocol for patients with COVID-19 of any severity, which allows it to have a decisive influence on the course of COVID-19, significantly improving the condition of patients, preventing the development of complications of coronavirus disease and the onset of death. A reasonable combination of sanogenetically, and etiopathogenetically oriented drugs, excluding disadvantages of polypharmacy, represents a new view and a promising therapeutic approach in the treatment of patients with COVID-19.

IV. Limitations

We did not initially plan to conduct scientific research, so our work in the context of the COVID-19 pandemic was exclusively clinical. In this regard, it has several limitations that must be considered when interpreting the results and conclusions. First, this work is not a randomized controlled trial (RCT), and therefore does not belong to the "golden standard" of clinical trials. Second, all clinical work and its results are descriptive, phenomenological, so there is an obvious potential for publication bias. This work provides a clinical benchmark for future targeted RCTs that will contribute to the overall COVID-19 treatment efforts.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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Oleg V. Bukhtoyarov was born 07.06.1966 in Rudny, Kazakhstan (USSR). Graduated from the S.M. Kirov Military Medical Academy in 1990 in Leningrad (now Saint Petersburg). MD in Psychoimmunology of cancer from the S.M. Kirov Military Medical Academy, 2012. The owner and chief physician of the Medical Center 39 Ltd, Kaliningrad, Russian Federation. Member of the Russian Society of Immunology.

Denis M. Samarin was born 22.07.1964 in Novosibirsk, USSR. Graduated from the Tomsk Military Medical Faculty at the Siberian State Medical University in 1987. PhD in Immunology from the Research Institute of Clinical Immunology SB RAMS, Novosibirsk, 1996. Head of the Laboratory of Psychoimmunology, Medical Center 39 Ltd, Kaliningrad, Russian Federation. Member of the Russian Society of Immunology.