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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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NEUROPROTECTIVE AND ANTIOXIDANT POTENTIAL OF MONTELUKAST-ACETYLCYSTEINE COMBINATION THERAPY FOR BRAIN PROTECTION IN PATIENTS WITH COVID-19 INDUCED PNEUMONIA

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Abstract.

Direct critical attack of the coronavirus on the alveoli and the excessive release of a large number of cytokines (IL-6, IL-1, TNF-α, etc.) provides suitable conditions for the further development of acute respiratory distress syndrome (ARDS) and severe acute respiratory failure. Serious decrease in blood oxygenation often lead to the deterioration of macro- and microcirculation, irreversible brain damage and hence, persistent neurological and mental disorders despite background intensive therapy and adequate respiratory support. Therefore, the aim of our open prospective observational study was to investigate the neuroprotective and antioxidant effectiveness of montelukast-acetylcysteine combination therapy for brain protection in patients with COVID-19 viral pneumonia.

A study was performed for five hundred seventy-eight (n=578) outpatients who were tested positive for novel coronavirus (SARS-CoV-2) by nasopharyngeal swap. The median age of patients was 62±17.45 years. In addition to clinical features and RT-PCR results, chest CT and chest X-ray (CXR) with high sensitivity were also very helpful for the early identification of viral pneumonia and COVID-19 disease assessment.

Considering the severity of Covid-19 pneumonia and the level of arterial oxygen saturation (transcutaneous hemoglobin oxygen saturation) on room air, all patients were divided into three major groups.

Group 1 (n=288) consisted of patients with a mild shift in oxygen saturation (SpO2 ≥ 95%) and well-defined pulmonary lesions (within 1-2 segments) without concomitant diseases; the second group (Group 2, n=250) included patients with clinical manifestations of moderate severity associated with a current saturation of 90-95% (SpO2) and small pulmonary lesions on chest X-ray in the presence of concomitant diseases: arterial hypertension (stage III) or CHF (FC / NYHA - 2), coronary heart disease or type 2 diabetes, cancer, tuberculosis, etc.

Most of the patients in third group (Group 3, n=48), during imaging studies, showed bilateral lung affection with low and peripheral distribution (with both - either ground glass opacities or multiple pulmonary nodules) and cardiomegaly. The respiratory failure of stage II-III (current oxygen saturation SpO2 75-90%), high respiratory rate (≥25 per minute), hemodynamic impairment (BP ≤ 100/60 mm Hg. Art., heart rate ≥125/min) were the most common objective clinical findings seen in this subset of patients. Laboratory changes included leukopenia less than 4.0x109/L or leukocytosis (≥10.0 X 109/L).

Background respiratory support with low-flow oxygen therapy and combined pharmacotherapy, where, along with montelukast and acetylcysteine, patients were prescribed a cephalosporin, a fluoroquinolone, an antifungal drug, a histamine blocker, an antiplatelet agent, a complex of B vitamins, led to a significant improvement in symptoms and laboratory parameters during the course of the disease.

The mean values of the blood biomarkers (CRP - 21.46±4.43 mg/l, LDH - 410.71±40.63 U/l, procalcitonin - 1.08±0.31 ng/ml, and ferritin - 270.43±27.23 ng/ml) return to normal by the 20th day after the fever subsides. Laboratory parameters before and after treatment course showed statistically significant differences between variables ($p<0.05$). No patient in Group 3 received JAK inhibitors (tofacitinib and baricitinib), IL-6 (olokizumab), IL-17A (netakimab) and glucocorticosteroids, however, recovery rates were completely good.

Assessment of the patient's neurological status (based on the NIHSS scores) revealed no signs of neurological changes.

Thus, based on the data given, it can be concluded that the high efficacy of the acetylcysteine/montelukast combination (as neuroprotectors) in pneumonia caused by COVID-19 is due to the effect of drugs on key mechanisms of pathogenesis: reduction of oxidative stress as drugs (combination) ensuring the free radical scavenging; stimulation of glutathione synthesis; suppression of cytokine storm; reduction of bronchospasm, mucus secretion and airway edema; lowering of BBB permeability and the ability to improve cerebral microcirculatory perfusion in the presence of antiplatelet agents.

In conclusion, the combination of montelukast and acetylcysteine may provide an effective, safe, multicomponent approach to the prevention of hypoxic brain injury in patients with COVID-19 pneumonia.

Key words. COVID-19, cytokine storm, acute respiratory distress syndrome, montelucast, N-Acetyl-L-cysteine (NAC), neuroprotection.

Introduction.

The clinical course of coronavirus infection and the outcome of the disease are largely determined by such factors as the virulence of the infectious agent, the comorbid status of the patient, the development of complications and the rational use of medications [2-8,11-12,14-17,30]. A classic complication of COVID-19 is viral pneumonia, which creates prerequisites for the development of acute respiratory distress syndrome (ARDS) and severe acute respiratory failure [8-12,18]. Even in intensive therapy and adequate respiratory support, impaired blood oxygenation often causes deterioration of macro- and microcirculation, irreversible brain damage and develops persistent neurological and mental disorders leading to further social disadaptation [8-12,23,25].

At the initial stage, the key link in pathogenesis is the coronavirus lesion of the alveoli (with severe disease courses) and the development of local inflammatory reaction [4-8]. In the focus of inflammation (as a response to viral invasion), epithelial cells, tissue macrophages and mast cells start releasing large

amounts of cytokines (IL-1, IL-6, tumor necrosis factor-α, etc.), increasing the recruitment of neutrophils, T-cells, macrophages and having a powerful destabilizing effect on the hemostatic system, vascular permeability and functioning of most organ systems [2-4,6,8-14,30]. Total damage of alveoli and secondary complications induced by "cytokine storm" (ARDS, DIC, thrombosis, thromboembolism, etc.) are often seen as one of the key causes for multiple organ failure and lethal outcomes, including among patients without significant comorbidities [12,35].

The pharmacological mechanism of action of montelukast is known to be based on antagonism to leukotriene receptors. Cysteinyl leukotrienes (CysLTs) are potent photogenic and immunomodulatory lipid mediators involved in inflammatory processes, including the "cytokine storm" and the acute phase of cerebral ischemia. Accordingly, CysLTs receptor antagonists "a priori" can provide suppression of the "cytokine storm" and protect the brain from ischemic damage. Montelukast (the drug has been recommended for use at all levels of bronchial asthma since 2002), on the one hand, eliminates bronchoconstriction and mucosal edema (induced by exposure to various triggers), and on the other hand, provides preservation of the BBB integrity under hypoxia and even reduces seizure frequency in patients with epilepsy [32]. According to Tesfaye B.A. et al. [32], montelukast showed neuroprotective effect on the basis of anti-inflammatory and antiapoptotic mechanisms of action. In experimental works on the model of global cerebral ischemia/reperfusion with bilateral carotid artery occlusion for 15 minutes followed by a 60-minute period of reperfusion, a favorable effect of montelukast was demonstrated on such biochemical parameters as lactate dehydrogenase activity, markers of oxidative stress (products of lipid peroxidation, nitric oxide and reduced glutathione), markers of inflammation (myeloperoxidase, tumor necrosis factor alpha, nuclear factor kappa-B, interleukin-6 and interleukin-10), biomarkers of apoptosis (caspase-3 and cytochrome C), neurotransmitters (glutamate, GABA), Cys-LT content and CysLT1 receptor expression [28,31]. Furthermore, montelukast inhibits platelet aggregation, which is important in thrombophilia [32].

It is well recognized that impaired blood oxygenation processes are almost always accompanied by rapid generation of excess free radicals (against the background of depletion of antioxidant systems resources) with subsequent damage of cell membranes and accumulation of fragments of destroyed cells [28-29]. Prophylactic use of acetylcysteine as an antioxidant and neuroprotector (cytoprotector), in the experiment - on the model of normobaric hypoxia, has inhibited the formation of reactive oxygen species (ROS) and highly toxic products of lipid peroxidation [29]. Acetylcysteine due to the presence of a free sulfhydryl group, directly neutralizes free radicals, on the other hand, by supplying cysteine for glutathione synthesis (whose content in cells largely determines the resistance of neurons to oxidative stress), it increases mitochondrial antioxidant activity [29].

It is generally considered that it is the increase of reduced glutathione (GSH) that provides antioxidant protection of cells and tissues [29]. Moreover, both forms of glutathione - oxidized and reduced - can also have a modulating effect on glutamate neurotransmission [29], since they are ligands for NMDA- and AMPA-receptors.

In view of the above, the purpose of the present open prospective observational study was to investigate the neuroprotective and antioxidant effectiveness of montelukast-acetylcysteine combination therapy for brain protection in patients with COVID-19 viral pneumonia.

Materials and Methods.

The study enrolled 578 patients with COVID-19, who could not be hospitalized (for objective reasons) in a pandemic. All patients had pneumonia caused by SARS-CoV-2 virus. The diagnosis of COVID-19 was confirmed anamnesthetically, clinically, radiologically and by a positive oropharyngeal smear test for SARS-CoV-2 performed by real-time polymerase chain reaction (PCR-RV). The mean age of the patients was 62±17.45 years. Given the severity of viral pneumonia and room air breathing saturation index, the patients were divided into three groups (see Table 1).

The first group (n=288) - mild degree (symptoms of intoxication were not observed, body temperature 37.5 - 39.5°C, respiratory failure ($SpO_2 \geq 95\%$) and hemodynamic disorders were absent, lung infiltration covered 1-2 segments, leukocytes 9.0-10.0 x 10^9/L with no concomitant diseases; the second group (n=250) - medium degree of severity (moderately expressed symptoms of intoxication, body temperature 37.5 - 39.5°C, pulmonary lesions within the limits of 2 segments, respiratory rate up to 25/min, shortness of breath, SpO_2 - 90-95%, heart rate - up to 100 bpm, increased sweating, with concomitant diseases such as hypertension (stage III), CHF (FK/NYHA-2), CHD, type 2 diabetes, cancer, tuberculosis, etc. The third group (n=48) - severe degree with body temperature >37,8C, respiratory insufficiency of II-III degree (SpO_2 75-90%), respiratory rate ≥ 25/min, hemodynamic instability (BP≤100/60 mm Hg, HR≥125/min), leukopenia less than 4.0 x 10^9/L or leukocytosis 10-20.0 x 10^9/L with more than 10% immature neutrophils, a frontal chest X-ray revealed increased heart size and multiple bilateral infiltrates (see Figure 1), multilobar, bilateral pneumonic

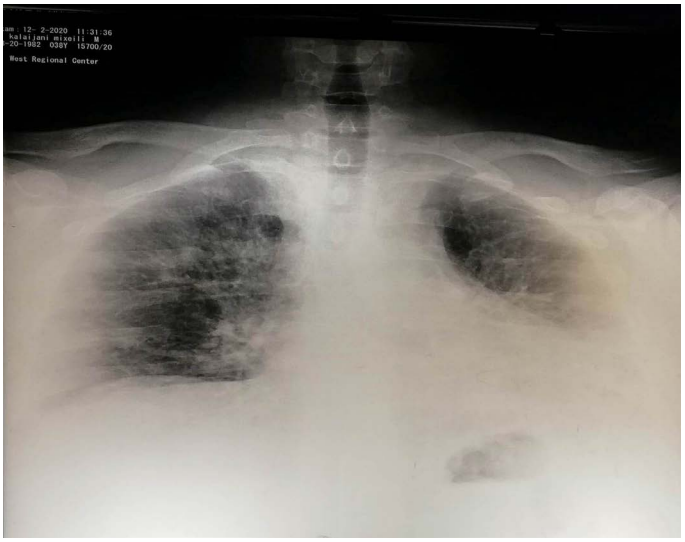

Figure 1. *Chest radiograph of a patient with progressive respiratory failure (severe disease course). Lung tissue thickening of low intensity bilaterally in the middle and lower parts of the right lung and upper parts of the left lung. Free fluid is detected in the left pleural cavity.*

Table 1. *Early warning scores (NEWS2 scale: 0-2 - satisfactory condition, 3-4 - moderate severity, 5-7 - severe condition).*

Severity Degrees	**T (^{0}C)**	**SpO_2 (%)**	**CRP (mg/L)**	**Fibrinogen**	**D - dimer**	**Ferritin**	**Procalcitonin**	**LDH**
Mild (Group 1, n=288)	< 38.5	95-100	≤20	N	N	N	N	N
Moderate (Group 2, n=250)	≤ 38.5	90- 95	20–50	< 4	1,5–2N	1,5–3N	1,5–2N	1,5–2N
Severe (Group 3, n=48)	38.5–40	75- 90	50–100	4–6	2–4N	3–6N	≥2N	2–4N

Table 2. *Combined pharmacotherapy (depending on the severity of the condition).*

	Group №1	**Group №2**	**Group №3**
Concomitant diseases	Without concomitant diseases	Hypertension (II - III stage), diabetes mellitus - type II, hypothyroidism, anemia, oncologic conditions, tuberculosis and etc.	Hypertension (III stage), CHF (NYHA class II), diabetes mellitus - type II, ischemic heart disease, oncologic conditions and etc.
Medications	Ceftriaxon – 1-2 g (i/m); Ciprofloxacin (500 mg) – *500 mg PO* bid. Vit. B complex - 1 tab. PO bid. Acetylcysteine (600 mg) - 1 tab. PO od. Ketotifen (1mg) – 1tab. bid. Montelucast (10 mg) - 1tab. PO od. Aspirine (500 mg) – half of tab. PO od.	Ceftriaxon – 1-2 g (i/m); Ciprofloxacin (500 mg) – *500 mg PO* bid. Vit. B complex - 1 tab. PO bid. Acetylcysteine (600 mg) - 1 tab. PO od. Ketotifen (1mg) – 1tab. bid. Montelucast (10 mg) - 1tab. PO od. Aspirine (500 mg) – half of tab. PO od. Fluconazole – 150 mg 1 caps. PO biw.	Ceftriaxon – 1-2 g (i/m); Ciprofloxacin (500 mg) – *500 mg PO* bid. Vit. B complex - 1 tab. PO bid. Vit. B_6 (5%-1 ml) – 1 ml od (i/m). Vit. C (5%-2 ml) – 2 ml od (i/m). Acetylcysteine (600 mg) - 1 tab. PO od. Ketotifen (1mg) – 1tab. PO od. Montelucast (10 mg) - 1tab. PO od. Fluconazole – 150 mg 1 caps. PO biw. Aspirine (500 mg) – half of tab. PO od.

infiltration accompanied by rapid progression of the process (increase in the infiltration area by 50% or more in 48 hours of follow-up, pleural effusion, failure of other organs and systems, impaired consciousness, exacerbation of concomitant diseases).

In all groups, medications were started from the moment of diagnosis of viral pneumonia (see Table 2) and continued for 48 hours, after body temperature normalized.

Of the antipyretics, the patient received either ibuprofen in a dose of 400 mg or aspirin in a dose of 500 mg, if necessary. Despite lack of appetite and severe weakness, all patients consumed protein- and vitamin-rich foods and, taking into account respiratory biomechanics, spent minimal time lying down (moving as intensively as possible).

The levels of C-reactive protein (CRP), ferritin, procalcitonin, D-dimer, and LDH, which is one of the markers of both tissue destruction and anaerobic respiration intensity, were studied as laboratory parameters reflecting the dynamics of the disease course and used to assess the activity of the inflammatory process [15-17,36].

During statistical processing of the results, $p < 0.05$ was deemed statistically significant. The mean data were estimated using Student's t-test [1].

Results and Discussion.

All patients with a positive oropharyngeal smear test for SARS-CoV-2 had anxiety, psychomotor agitation, and panic attacks of varying degrees before starting treatment. After talking to medical personnel, the internal tension was relieved in most patients (without medical intervention), but in some patients (25%) the state of anxiety persisted until normalization of body temperature (up to 22 days in single cases). In group N1, the disease was mild for 10 - 14 days. Patients in this category did not present complications and evolved clinically well.

At the onset of the disease, most patients had a rise in body temperature to 37.5°C in the morning and to 38.5°C in the evening. In 2-5 days from the onset of fever, other signs were observed: cough, dry or with poor sputum, shortness of breath, chest congestion, sore throat, weakness, headache, anosmia, dysgeusia, anorexia. Pulmonary infiltration within 1-2 segments was recorded on days 5-7 after the manifestation of signs of acute respiratory infection, which was a predictor for the initiation of antibiotic therapy (Table N2). As is known, "viral pneumonia" can be of varying severity, but the patient does not always need to be prescribed antimicrobial agents [19-20]. However, viral invasion in COVID-19 creates conditions for secondary bacterial infection (Streptococcus pneumoniae, Staphylococcus aureus (MSSA, MRSA), Haemophilus influenza) and the "wait-and-see" tactics (considering the increase in CRP) are not justified [22,33-34].

In the clinical blood test, elevated ESR (CRP) was observed in all patients, neutropenia only in 34.92%. Normalization of body temperature was an indicator of positive dynamics (against the background of pharmacotherapy). Fever duration (group N1) did not exceed 14 days. Stabilization of the process began, on average, from the 10th day after infection. No deviations were observed in the neurological status of patients (group N1). Dry cough was prevalent symptom in the post-infection period, which was managed by a combination of prenoxdiazine (under the brand name Libexin), montelukast and aminophylline in

therapeutic doses. Recovery of taste and smell took an interval of 2 to 10 weeks. No lethal outcomes were observed in group N1.

Characteristic markers of COVID-19 severity in group N2 were prolonged fever, decreased blood oxygen saturation, lung CT pattern, decreased lymphocyte count, increased levels of D-dimer, CRP, fibrinogen, ferritin, LDH, etc. According to the protocol, taking into account the age and comorbid status of patients (obesity, diabetes, heart disease, etc.), a combination of cytokine inhibitor /JAK-kinase/ and glucocorticosteroids should have been prescribed to suppress the "cytokine storm". However, given the mechanism of action, contraindications, and life-threatening side effects of these drugs (tofacitinib, baricitinib, methylprednisolone, dexamethasone, etc.) we refused to use them [27,32,36]. It should be emphasized that in all groups, only montelukast and acetylcysteine were administered to overcome the "cytokine storm". To improve blood oxygenation (28 patients out of 250), prone position and minimal respiratory support with low-flow oxygen (oxygen flow 3-6 L/min for no more than 7 days) were recommended [18,21,24,26]. Despite the fact that 8 patients from this group had a history of urogenital oncopathology and were in clinical remission, the course of the infectious process in them did not differ from that in the same group of patients without significant comorbidities. In two individuals the development of pneumomediastinum was not accompanied by deterioration of the condition and resolved without surgical intervention. All patients of group N2 recovered. There were no deviations from the norm in the neurological status.

All patients in group N3 were severe. High fever (up to 40.5°C), tachycardia, increased sweating, dyspnea - 25-30 breaths per minute with involvement of auxiliary muscles, dry cough, respiratory failure stage II-III (SpO_2 - 75-90%), cyanosis on exertion, severe weakness (they had difficulty moving and talking), an increased heart size on a frontal chest X-ray, multiple bilateral infiltrates were more prevalent on examination in severe cases (see Figure 2). Computed tomography of the chest organs revealed pulmonary bilateral interstitial changes in the form of ground - glass opacities, pleural effusion, etc. Lung tissue lesion was at least 50%. Before the start of treatment, significant biological abnormalities were observed mainly in laboratory parameters: neutropenia (0.8±0.11×109/L), lymphocytopenia (0.85±0.09×109/L), leukopenia (3.1±1.02×109/L), increased fibrinogen (7.9±2.61 g/L), C-reactive protein (93.96±11.13 mg/L), ferritin (1105.58±53.19 ng/mL), D-dimer (859.96±150.13 ng/mL), LDH (735.71±20.23 units/L) and procalcitonin (6.78±1.22 ng/mL). In group N3, skeletal muscle weakness reached its maximum on days 12-17 from the manifestation of COVID-19. Patients could not even sit or stand up on their own. They refused to eat. Respiratory support with low-flow oxygen (oxygen flow 3-6 l/min for no more than 10 days) was used to increase blood oxygenation (in 26 patients out of 48). Studies have shown that with normal cardiac output SpO_2 can be below 22 mmHg without the development of lactic acidosis, but with impaired hemodynamics, blood lactate concentration increases rapidly, as blood flow is considered a critical determinant of oxygenation. It is worth noting that during oxygen therapy, increasing the concentration of oxygen in arterial blood leads to

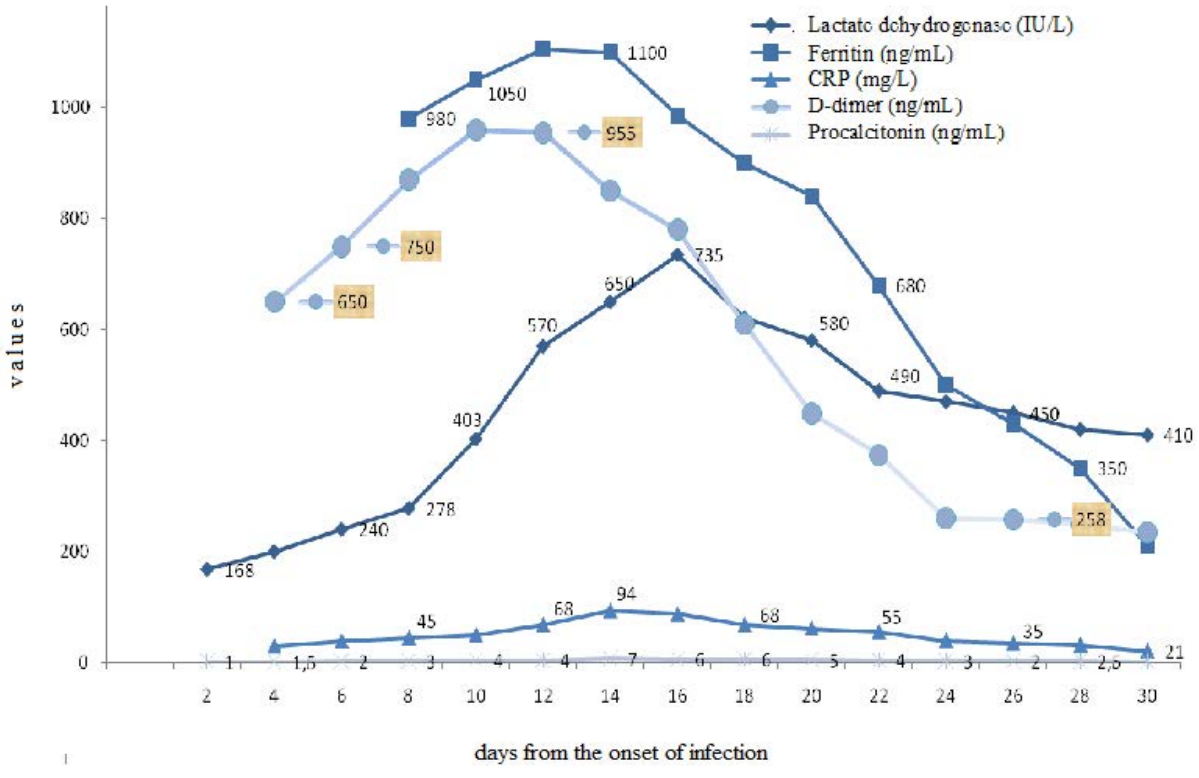

Figure 2. *Dynamics of LDH, CRP, ferritin, D-dimer and procalcitonin in patients with severe COVID-19 (group N3).*

a decrease in cardiac output and thus does not always improve tissue oxygenation.

Four (of 48) patients had an enlarged liver and moderate hypertransaminasemia (ALT, AST, GGT). The mechanisms of liver damage in COVID-19 are not fully understood, but it is likely that decreased oxygenation and impaired hemodynamics can contribute to increased liver vulnerability in critically ill patients. Further, against the background of treatment of the underlying disease (COVID-19) with acetylcysteine and B vitamins, a decrease in the concentration of transaminases and normalization of enzymes in the blood were noted (on average after 3-4 weeks). In addition, we observed laboratory features associated with the positive dynamics of the disease course. C-reactive protein (21.46±4.43 mg/L), ferritin (270.43±27.23 ng/mL), D-dimer (235.55±48.13 ng/mL), LDH (410.71±40.63 units/L) and procalcitonin (1.08±0.31 ng/mL) improved on average 20 days after fever disappeared (Figure 1). Differences in laboratory values before and after treatment were statistically significant ($p<0.05$). All patients in group N3 recovered without the use of JAK-kinase inhibitors (tofacitinib and baricitinib), IL-6 (olokizumab), IL-17A (netakimab) and glucocorticosteroids. No abnormalities were observed in the patients' neurological status (as assessed by the NIHSS scale).

Conclusion.

Summarizing the data obtained, we can conclude that the high effectiveness of montelukast and acetylcysteine in viral COVID-19 pneumonia is associated with their effects on the key events of pathogenesis: inhibition of free radical formation, stimulation of glutathione synthesis, suppression of "cytokine storm", elimination of bronchoconstriction and mucosal edema, reduction of permeability of the blood-brain barrier and improvement of microcirculation amid antiaggregative effect. Accordingly, the combination of montelukast and acetylcysteine can be used to prevent hypoxic brain damage and improve survival of patients with viral pneumonia.

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РЕЗЮМЕ

НЕЙРОПРОТЕКТОРНЫЙ И АНТИОКСИДАНТНЫЙ ПОТЕНЦИАЛ КОМБИНИРОВАННОЙ ТЕРАПИИ МОНТЕЛУКАСТОМ И АЦЕТИЛЦИСТЕИНОМ ДЛЯ ЗАЩИТЫ МОЗГА У ПАЦИЕНТОВ С ПНЕВМОНИЕЙ, ВЫЗВАННОЙ COVID-19

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Поражение альвеол коронавирусом и выброс большого количества цитокинов (IL-6, IL-1, TNF–α и т.д.) создает условия для развития острого респираторного дистресс-синдрома (ОРДС) и выраженной острой дыхательной недостаточности. Даже на фоне интенсивной терапии и адекватной респираторной поддержки, нарушение процессов оксигенации крови часто становится причиной ухудшения макро- и микроциркуляции, необратимого повреждения головного мозга и развития стойких неврологических и психических нарушений. Поэтому, целью настоящего открытого проспективного наблюдения явилось сравнительное изучение нейропротекторной и антиоксидантной активности комбинации монтелукаста (в суточной дозе 10 мг) и ацетилцистеина (в суточной дозе 600 мг) для защиты мозга у больных с вирусной пневмонией на фоне COVID-19. В исследование включено 578 больных с COVID-19, которых в условиях пандемии, не удалось госпитализировать (по объективным причинам). Все больные пневмонией, вызванной вирусом SARS-CoV-2. Диагноз COVID-19 был подтвержден положительным результатом исследования орофарингеального мазка на SARS-CoV-2. Средний возраст больных составил 62±17,45 года. С учетом состояния тяжести течения вирусной пневмонии и показателя сатурации при дыхании комнатным воздухом, больные были разделены на три группы. Первая группа (n=288) – лѐгкая степень ($SpO_2 \geq 95\%$), легочная инфильтрация в пределах 1-2 сегментов, нет сопутствующих заболеваний; вторая группа (n=250) - средняя степень тяжести (легочная инфильтрация в пределах 2 сегментов, SpO_2 – 90-95%, имеются сопутствующие заболевания - гипертоническая болезнь (III стадия), ХСН (ФК/NYHA - 2), ИБС, СД 2 типа, онкозаболевания, туберкулез и т.д.; третья группа (n=48) – тяжелая степень (дыхательная недостаточность II-III ст (SpO_2 75-90%), частота дыхания ≥ 25/мин. нарушения гемодинамики (АД≤100/60 мм рт. ст, ЧСС ≥ 125/мин), лейкопения менее 4,0 х 10^9/л или лейкоцитоз ≥10,0 х 10^9/л, на фронтальной рентгенограмме увеличение размеров сердца и многочисленные билатеральные инфильтраты, многодолевая, двусторонняя пневмоническая инфильтрация и т.д. На фоне респираторной поддержки с низкопоточным кислородом и проведения комбинированной фармакотерапии, которая кроме монтелукаста и ацетилцистеина включала цефалоспорин, фторхинолон, противогрибковое средство, гистаминоблокатор, антиагрегант и витамины группы В, отмечено существенное изменение в лабораторных показателях, отражающих динамику течения заболевания. Нормализация содержания С-реактивного белка (21,46±4,43 мг/л), ферритина (270,43±27,23 нг/мл), D-димера (235,55±48,13 нг/мл), ЛДГ (410,71±40,63 ед/л) и прокальцитонина (1,08±0,31 нг/мл) происходила в среднем через 20 дней после исчезновения лихорадки. Различия

в лабораторных показателях до- и после лечения были статистически достоверными (p<0,05). Все пациенты из группы N3 выздоровели, без применения ингибиторов JAK-киназ (тофацитиниб и барицитиниб), ИЛ-6 (олокизумаб), ИЛ-17А (нетакимаб) и глюкокортикостероидов. В неврологическом статусе пациентов отклонений от нормы не наблюдали (оценивали по *шкале NIHSS)*. На основании полученных данных можно заключить, что высокая эффективность комбинации ацетилцистеина и монтелукаста (как нейропротекторов) на фоне вирусной пневмонии при COVID-19, связана с влиянием препаратов на ключевые звенья патогенеза: ингибирование образования свободных радикалов, стимуляция синтеза глутатиона, подавление «цитокинового шторма», устранение бронхоконстрикции и отека слизистой оболочки, снижение проницаемости гематоэнцефалического барьера и улучшение микроциркуляции на фоне антиагрегационного эффекта. Соответственно, комбинация монтелукаста и ацетилцистеина может быть использована для предотвращения гипоксических повреждений мозга у больных с вирусной пневмонией.

Key words: COVID-19, цитокиновый шторм, острый респираторный дистресс-синдром, монтелукаст, ацетилцистеин, нейропротекция.

SUMMARY

NEUROPROTECTIVE AND ANTIOXIDANT POTENTIAL OF MONTELUKAST-ACETYLCYSTEINE COMBINATION THERAPY FOR BRAIN PROTECTION IN PATIENTS WITH COVID-19 INDUCED PNEUMONIA

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Direct critical attack of the coronavirus on the alveoli and the excessive release of a large number of cytokines (IL-6, IL-1, TNF-α, etc.) provides suitable conditions for the further development of acute respiratory distress syndrome (ARDS) and severe acute respiratory failure. Serious decrease in blood oxygenation often lead to the deterioration of macro- and microcirculation, irreversible brain damage and hence, persistent neurological and mental disorders despite background intensive therapy and adequate respiratory support. Therefore, the aim of our open prospective observational study was to investigate the neuroprotective and antioxidant effectiveness of montelukast-acetylcysteine combination therapy for brain protection in patients with COVID-19 viral pneumonia.

A study was performed for five hundred seventy-eight (n=578) outpatients who were tested positive for novel coronavirus (SARS-CoV-2) by nasopharyngeal swap. The median age of patients was 62±17.45 years. In addition to clinical features and RT-PCR results, chest CT and chest X-ray (CXR) with high sensitivity were also very helpful for the early identification of viral pneumonia and COVID-19 disease assessment.

Considering the severity of Covid-19 pneumonia and the level of arterial oxygen saturation (transcutaneous hemoglobin oxygen saturation) on room air, all patients were divided into three major groups.

Group 1 (n=288) consisted of patients with a mild shift in oxygen saturation ($SpO_2 \geq 95\%$) and well-defined pulmonary lesions (within 1-2 segments) without concomitant diseases; the second group (Group 2, n=250) included patients with clinical manifestations of moderate severity associated with a current saturation of 90-95% (SpO_2) and small pulmonary lesions on chest X-ray in the presence of concomitant diseases: arterial hypertension (stage III) or CHF (FC / NYHA - 2), coronary heart disease or type 2 diabetes, cancer, tuberculosis, etc.

Most of the patients in third group (Group 3, n=48), during imaging studies, showed bilateral lung affection with low and peripheral distribution (with both - either ground glass opacities or multiple pulmonary nodules) and cardiomegaly. The respiratory failure of stage II-III (current oxygen saturation SpO_2 75-90%), high respiratory rate (≥25 per minute), hemodynamic impairment (BP ≤ 100/60 mm Hg. Art., heart rate ≥125/min) were the most common objective clinical findings seen in this subset of patients. Laboratory changes included leukopenia less than $4.0x10^9$/L or leukocytosis ($\geq 10.0 \times 10^9$/L).

Background respiratory support with low-flow oxygen therapy and combined pharmacotherapy, where, along with montelukast and acetylcysteine, patients were prescribed a cephalosporin, a fluoroquinolone, an antifungal drug, a histamine blocker, an antiplatelet agent, a complex of B vitamins, led to a significant improvement in symptoms and laboratory parameters during the course of the disease.

The mean values of the blood biomarkers (CRP - 21.46±4.43 mg/l, LDH - 410.71±40.63 U/l, procalcitonin - 1.08±0.31 ng/ml, and ferritin - 270.43±27.23 ng/ml) return to normal by the 20th day after the fever subsides. Laboratory parameters before and after treatment course showed statistically significant differences between variables (p<0.05). None patient in Group 3 received JAK inhibitors (tofacitinib and baricitinib), IL-6 (olokizumab), IL-17A (netakimab) and glucocorticosteroids, however, recovery rates were completely good.

Assessment of the patient's neurological status (based on the NIHSS scores) revealed no signs of neurological changes.

Thus, based on the data given, it can be concluded that the high efficacy of the acetylcysteine/montelukast combination (as neuroprotectors) in pneumonia caused by COVID-19 is due to the effect of drugs on key mechanisms of pathogenesis: reduction of oxidative stress as drugs (combination) ensuring the free radical scavenging; stimulation of glutathione synthesis; *suppression* of *cytokine storm*; reduction of *bronchospasm*, *mucus* secretion and airway *edema*; *lowering of BBB permeability* and the ability *to improve cerebral microcirculatory* perfusion in the presence of antiplatelet agents.

In conclusion, the combination of montelukast and acetylcysteine may provide an effective, safe, multicomponent approach to the prevention of hypoxic brain injury in patients with COVID-19 pneumonia.

Key words: COVID-19, cytokine storm, acute respiratory distress syndrome, montelucast, N-Acetyl-L-cysteine (NAC), neuroprotection. **reziume montelukastis da acetilcisteinis kombinirebuli Terapiis neiroproteqtoruli da antioqsidanturi**

potenciali (Tavis tvinis iSemiisgan dacvis mizniT) COVID-19-iT gamowveuli virusuli pnevmoniis mqone pacientebSi

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koronavirusiT alveolebis dazianeba da didi raodenobiT citokinebis (IL-6, IL-1, TNF–α da a.S.) gamotyorcna qmnis winapirobebs mwvave respiratoruli distres-sindromis da sunTqvis mwvave ukmarisobis ganviTarebisaTvis. sisxlis oqsigenaciis procesebis darRveva, intensiuri Terapiis da adekvaturi respiratoruli mxardaWeris fonzec ki, xSirad gvevlineba rogorc makro- da mikrocirkulaciis gauaresebis, aseve Tavis tvinis Seuqcevadi dazianebis da gamoxatuli nevrologiuri da fsiqikuri darRvevebis ganviTarebis mizezad. Aamitom, Ria prospeqtiuli dakvirvebis mizani iyo COVID-19-is fonze ganviTarebuli virusuli pnevmoniis mqone pacientebSi, montelukastis (sadReRamiso doza - 10mg) da acetilcisteinis (sadReRamiso doza – 600 mg) kombinaciis neiroproteqtoruli da antioqsidanturi aqtivobis Seswavla. kvlevaSi CarTuli iyo 578 kovidinficirebuli pacienti, romelTa hospitalizacia (pandemiis pirobebSi) ver moxerxda obieqturi mizezebis gamo. Yyvela pacients hqonda virusuli pnevmonia gamowveuli SARS-CoV-2 (testis pasuxi orofaringealuri nacxis gamokvlevisas SARS-CoV-2-ze iyo dadebiTi). pacientebis saSualo asakma Seadgina 62±17.45w. virusuli pnevmoniis mimdinareobis simZimis da saturaciis maCveneblis (oTaxis haeris SesunTqvis pirobebSi) gaTvaliswinebiT, pacientebi gavanawileT 3 jgufSi: I jgufi (n=288) – pnevmoniis msubuqi mimdinareoba, SpO_2 ≥ 95%, filtvebis rentgenologiuri gamokvlevisas aRiniSneboda infiltracia 1-2 segmentSi, pacientebs Tanmxlebi daavadebebi ar hqondaT; II jgufi (n=250) – simZimis saSualo xarisxi, SpO_2 – 90-95%, infiltracia 1-2 segmentSi, Tanmxlebi daavadebebidan hipertonuli daavadeba (III stadia), gulis qronikuli ukmarisoba (NYHA - 2), gulis iSemiuri daavadeba, Saqriani diabeti (II tipis), onkopaTologiebi, tuberkulozi da a.S.; III jgufi (n=48) – infeqciuri procesis mZime mimdinareoba (II-III xarisxis sunTqvis ukmarisoba), SpO_2 75-90%, sunTqvis sixSire ≥ 25/wT, hemodinamikis darRveva (arteriuli wneva ≤100/60 mm. vwy. svetis mixedviT, guliscemis sixSire ≥ 125/wT), leikopenia (≤4,0 x 10^9 /l) an leikocitozi (≥10,0 x 10^9/l), frontalur rentgenogramaze gulis sazRvrebis gadideba, mravalricxovani bilateraluri infiltratebi da a.S.. respiratoruli mxardaWeris da kombinirebuli farmakoTerapiis pirobebSi, romelic montelukastis da acetilcisteinis garda, moicavda cefalosporins, ftorqinolons, antimikozur saSualebas, histaminoblokators, antiagregants da B-jgufis vitaminebs, dafiqsirda arsebiTi xasiaTis cvlilebebi daavadebis mimdinareobis amsaxvel laboratoriul maCveneblebSi. C – reaqtiuli proteinis (21,46±4,43 mg/l), feritinis (270,43±27,23 ng/ml), D – dimeris (235,55±48,13 ng/ml), laqtatdehidrogenazas (410,71±40,63 me/l) da prokalcitoninis (1,08±0,31 ng/ml) Semcvelobis normalizacia xdeboda cxelebis gaqrobidan saSualod 20 dRis Semdeg. sxvaoba laboratoriul maCvenebelebSi (monacemebis statistikuri damuSavebisas) mkurnalobis dawyebamde da dawyebis Semdeg iyo sarwmuno ($p<0.05$). yvela pacienti III jgufidan gamojanmrTelda JAK-kinazas inhibitorebis (tofacitinibi, bricitinibi), interleikin–6-is (olokizumabi) da interleikin-17-is (netakimabi) inhibitorebis da glukokortikosteroidebis gamoyenebis gareSe. pacientebis nevrologiur statusSi normidan gadaxra ar dafiqsirebula (Sefasebis *NIHSS-is skalis mixedviT)*.

miRebuli Sedegebis safuZvelze SegviZlia davaskvnaT, rom acetilcisteinis da montelukastis kombinaciis maRali efeqturoba (rogorc neiroproteqtorebis) COVID-19-iT gamowveuli virusuli pnevmoniis fonze, dakavSirebulia am wamlebis zemoqmedebasTan paTogenezis sakvanZo rgolebze: Tavisufali radikalebis warmoqmnis inhibirebasTan, “citokinuri Stormi”-s daTrgunvasTan, bronqokonstriqciis da lorwovani garsis SeSupebis xarisxis SemcirebasTan, hematoencefaluri barieris ganvladobis SemcirebasTan da mikrocirkulaciis gaumjobesebasTan (antiagregaciuli efeqtis gamo). Sesabamisad, montelukastis da aceilcisteinis kombinacia, SesaZloa gamoyenebuli iqnas hipoqsiiT ganpirobebuli Tavis tvinis dazianebebis asacileblad.

Key words: COVID-19, citokinuri Stormi, mwvave respiratoruli distress - sindromi, montelukasti, acetilcixteini, neiroproteqcia.