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Proactive antiinflammatory and anticoagulant therapy in the treatment of advanced stages of novel coronavirus infection (COVID-19). Case Series and Study Design: COLchicine versus ruxolitinib and secukinumab in Open prospective RandomIzed Trial (COLORIT)

The article is devoted to the treatment of the new coronavirus infection (COVID-19) in the advanced stages of the disease. The types of response of the immune system to the viral load of SARS-CoV-2 with the start of the inflammation process are considered. The situation is analyzed in detail in which the growing autoimmune inflammation (up to the development of a «cytokine storm») affects not only the pulmonary parenchyma, but also the endothelium of the small vessels of the lungs. Simultaneous damage to the alveoli and microthrombosis of the pulmonary vessels are accompanied by a progressive impairment of gas exchange, the development of acute respiratory distress syndrome, the treatment of which, even with the use of invasive ventilation, is ineffective and does not really change the prognosis of patients with COVID-19. In order to interrupt the pathological process at the earliest stages of the disease, the necessity of proactive anti-inflammatory therapy in combination with active anticoagulation treatment is substantiated. The results of the first randomized studies on the use of inhibitors of pro-inflammatory cytokines and chemokines (interleukin-6 (tocilizumab), interleukin-17 (secukinumab), Janus kinase blockers, through which the signal is transmitted to cells (ruxolitinib)), which have potential in the early treatment of COVID- 19. The use of a well-known anti-inflammatory drug colchicine (which is used for gout treatment) in patients with COVID-19 is considered. The design of the original COLORIT comparative study on the use of colchicine, ruxolitinib and secukinumab in the treatment of COVID-19 is presented. Clinical series presented, illustrated early anti-inflammatory therapy together with anticoagulants in patients with COVID-19 and the dangers associated with refusing to initiate such therapy on time.

Keywords COVID-19; cytokine storm; colchicine; ruxolitinib; secukinumab; anti-inflammatory therapy; anticoagulant therapy

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Under the continuing worldwide increase in the incidence of the novel coronavirus 2019 disease (COVID-19), with around 4% mortality, and enormous challenges in treating patients with severe bilateral viral pneumonia, it has become apparent that rational approaches to managing this disease at different stages of its progression are required. Of those infected with SARS-CoV-2, about 40% of patients are asymptomatic virus carriers, approximately another 25% have a mild form of the disease and do not need hospitalization [1]. However, a third of patients have such complications as specific viral pneumonia, which prompts the search for effective therapy. Of the hospitalized patients with moderate to severe disease, about 10% require intensive care and 5% require invasive ventilation (IV). In-hospital mortality reaches 10% or more and increases with age and several comorbidities [1].

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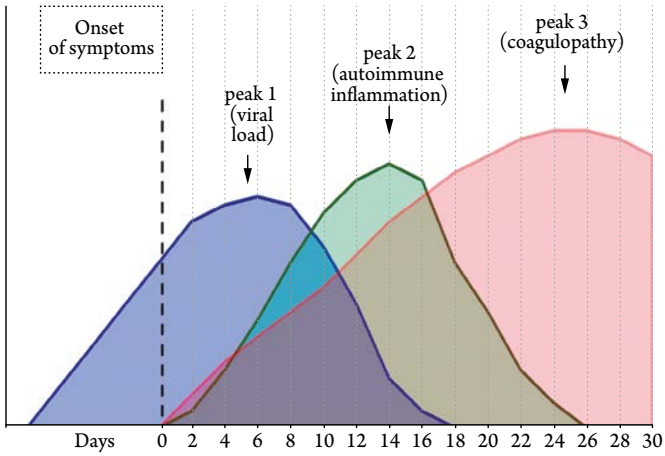
Figure 1. Development of various presentations of the new coronavirus disease (days of the disease)



A total of 424 patients with coronavirus pneumonia were treated at the Medical Research and Educational Center (Lomonosov University Clinic) from April 21 to June 13, 2020: 48 (11.3%) patients stayed in the intensive care unit, 24 patients (50% of ICU patients and 5.7% of all patients) were put on IV, which was generally consistent with worldwide statistics [2–4].

Of those, four (0.94%) patients died, the mean age was 78 ± 8 (72–86) years, all had three or more comorbidities. It should be noted that another ten patients were transferred to other hospitals due to the closure of the COVID-hospital in the Lomonosov University Clinic, and five of them died in other hospitals. The oldest discharged patient with bilateral viral and bacterial pneumonia was 97 years old. The stage-by-stage progression of the new coronavirus disease is shown in Figure 1.

At the first stage (blue line in Figure 1), most of the negative impact is due to viral load, which begins before the first symptoms appear and leads to the first early peak of mortality (end of week one of the disease). This is the most dangerous period for elderly and senile obese patients with comorbidities, such as cardiovascular pathologies, diabetes mellitus, lung and kidney diseases. The prognosis was particularly low in patients who discontinue conventional therapy, primarily renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, and modern antidiabetic drugs, and who do not control optimal blood pressure (BP), cholesterol, and glucose levels [5–7]. During this period, the focus is on the earliest use of antiviral drugs and agents that prevent the virus from entering the cell, which was discussed in a dedicated article [8].

In this article, we analyze the attempts to approach the best possible combination therapy for the new coronavirus disease at advanced stages, when the use of anti-inflammatory therapy and anticoagulants takes center stage.

After days 7–10 of the disease, other factors (other than viremia) are more involved in its progression and poor prognosis for patients. The disease is expected to progress at this period, if in visible well-being and slightly decreased blood oxygen saturation, the body temperature remains subfebrile, there is still a sense of dyspnea, asthenia, and most importantly lymphopenia persists or progresses; there is even a non-critical increase in C-reactive protein (CRB) and interleukin-6 (IL-6) levels. As can be seen in Figure 1, other factors emerge at this time: a gradually increasing inflammation (green line), which overloads the immune system, causes a sharp increase in the production of cytokines stimulating the development of infiltrative fibrosis, exudative solidification of pulmonary tissue, desquamation of lung epithelial cells, and loss of aeration of the alveoli [9]. This condition resembles more the onset of alveolitis than true pneumonia. Alveoli drown, and the lungs lose the ability to exchange gases. Pulmonary tissue becomes airless and pronouncedly swollen with atelectasis areas [10]. In such cases, even mechanical ventilation is useless.

Figure 2 shows the types of cytokine-mediated immune reactions and inflammation during the new coronavirus disease.

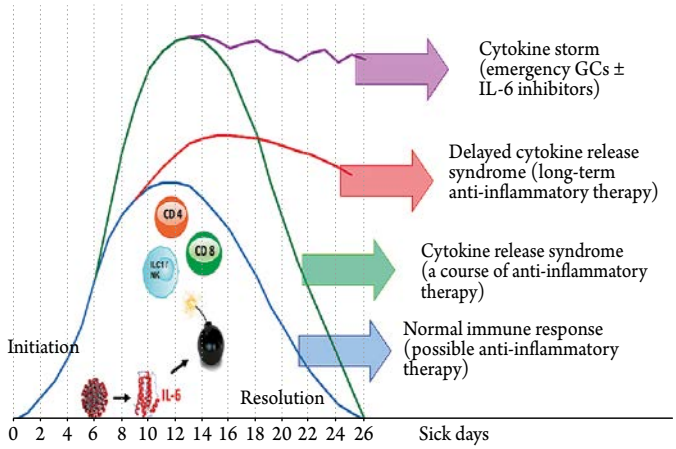
The normal immune response (blue line in Figure 2) allows the body to cope with increasing inflammation gradually. The most significant risk falls on days 10–14 of the disease [11, 12]. In relatively young patients without comorbidities, it may result in moderate pulmonary lesions (stages 1–2 according to the Classification of the Ministry of Healthcare of the Russian Federation) such as ground-glass nodules with reduced aeration but with alveoli still capable of gas exchange [13]. These patients can usually clear the infection without anti-inflammatory therapy, but the risk of pneumonia cannot be eliminated [14, 15]. However, early anti-inflammatory therapy helps them suppress infection more quickly and avoid prolonged asthenia and recovery. Mortality is less than 1% in such patients, the same as of seasonal flu.

If inflammation persists and there is no improvement by day 10 of the disease, an exaggerated immune response is possible (green line in Figure 2), which is called cytokine release syndrome [14, 16]. A rapid (sometimes instantaneous) progression of the pulmonary lesions occurs, which appears as a crazy-paving pattern, i.e., irregular opacities in various ground-glass areas with the progression to consolidation. This indicates a gradual loss of aeration [17]. The post-mortem examinations of patients who had died of COVID-19 identified the cellular fiber-myxoid exudates in the consolidation areas [18]. Such patients require emergency proactive anti-inflammatory therapy, which changes the course quickly

enough within 5–7 days and can prevent the patient's transfer to the ICU and being put on ventilation, which should be the treatment goal in COVID-19. Continuous oxygen support, prone positioning for as long as possible, and careful introduction of respiratory actions make a valuable contribution. Thus, such an approach was dynamically used in Lomonosov University Clinic [19]. Mortality in this group of patients is 2–3% and can be reduced by the timely start of anti-inflammatory therapy. The end of week two and the beginning of week three of the disease are the most critical period (red line in Figure 1).

This critical course is possible in elderly and senile patients and specifically in male patients with overweight, diabetes mellitus, cardiovascular and pulmonary diseases [20, 21]. This is a delayed cytokine release syndrome (red line in Figure 2). Activation of IL-6 and other pro-inflammatory cytokines and chemokines in response to the entrance of SARS-CoV-2 into alveolar epithelial cells leads to vigorous stimulation of the CD-4 and CD-8 lymphocytes as a protective reaction [22]. It is accompanied by the onset of lymphopenia, the severity of which allows the most accurate diagnosis of the disease severity, and even the prognosis for patients [23]. Granulocytes accumulate in the lesions (small bronchi and alveoli) as neutrophilic and macrocytic infiltration [16]. High neutrophil levels are detected in the blood, as well as a continuing decrease in lymphocyte count. In this case and after day 15 of the disease, viral pneumonia steadily progresses as the volume of the pulmonary parenchymal lesions increases despite all efforts [24]. Even proactive anti-inflammatory therapy changes the situation very slowly in such patients. A large area of lesion remains on control MSCT scans for a long time [25]. Dyspnea, low blood oxygen saturation, asthenia persist for up to four weeks. The aforementioned sometimes reaches extreme severity. Continuous oxygen therapy is needed in such cases. If possible, patients should be prone, which makes breathing deeper and improves ventilation of the posterior segments of the lungs. Nevertheless, some patients require emergency anti-inflammatory therapy with IL-6 receptor inhibitors or glucocorticoids (GCs). Transfer to the ICU and putting on ventilation often results in a week or more of ventilation. Intensivist skills are the key to preventing hospital-acquired infection. Patients should be transferred to non-invasive ventilation and spontaneous breathing as soon as possible, which was also a fundamental rule in the Lomonosov University Clinic. About 14% of hospitalized patients with COVID-19 are transferred to the ICU in the United States and Europe, and 12.2% (!) of patients are put on ventilation, which corresponds to 80–90% of all ICU

Figure 2. Autoimmune inflammation in COVID-19 and the possibility of anti-inflammatory therapy (see details in the text)



GCs, glucocorticosteroids, Il-6, interleukin type 6.

patients; mean duration of ventilation is 12 to 18 days [26–28]. Such overactive management potentially may determine higher mortality rates than those in China and the Russian Federation. Mortality reaches 10–15% in this group of patients.

Finally, the critical development of events, such as a persistent progression of autoimmune inflammation, was called a cytokine storm (lilac line in Figure 2). Cytokine storm involves an acute activation of IL-6 and other pro-inflammatory cytokines and chemokines, a multifold increase in CRB, a decreased lymphocyte count and an increased neutrophil count and progressing acute respiratory distress syndrome (ARDS) [29, 30]. This all results in a total lesion of both lungs in the form of pneumonitis (heavy, drowning lungs), which is manifested by progressing ARDS and accompanied by an unfavorable prognosis for patients with COVID-19 [10]. Patients stay in the ICU for a long time (up to a month or more) and are ventilated for several weeks. Such complications as pneumothorax or pneumomediastinum are not uncommon [31, 32]. We observed five unique cases of spontaneous pneumothorax and/or pneumomediastinums in critical patients on long-term ventilation; these cases require a separate discussion. In critical cases, even the most proactive anti-inflammatory therapy with tocilizumab (a seeming panacea) and high-dose GCs does not always stop the progression of the disease and lead to successful treatment of viral pneumonia [33]. SARS-CoV-2 affects not only the lungs but also other organs and systems (heart, kidneys, pancreas, and even the brain) [9, 34, 35]. In these cases, severe ARDS is accompanied by the onset and progression of multiple organ failure (myocarditis, heart failure, kidney failure, exacerbation of diabetes mellitus). According to the global statistics, mortality in such patients varies from 50–60 to 80–90%,

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depending on the ventilation efforts and duration [26, 36]. The third peak of mortality (red line in Figure 1) falls on days 25–30 of the disease.

Given the above types of disease progression, it is important to be aware of the clinical manifestations of the disease, which allow the adverse course to be assessed to initiate specific anti-inflammatory therapy as early as possible. These manifestations include worsening of the clinical condition in the form of continuing fever, persistent dyspnea and the sensation of chest congestion, occasional exhausting cough, low blood oxygen saturation, mandatory oxygen support, and progressing bronchial asthma. On the basis of our experience, persistently decreased lymphocyte count, increased levels of neutrophils, CRB, and especially IL-6 are a warning sign for the progression of viral pneumonia (pneumonitis) during the second week of the disease, which requires proactive anti-inflammatory therapy.

A lymphocyte count is the simplest and most informative criterion for distinguishing patients with either a mild, moderate, or critical course of COVID-19 [23]. Their absolute count and changes over time should be closely monitored during the observation and treatment of patients.

It is worth noting that there are two additional easily calculated variables, as well as an essential assessment of the changes in lymphocyte count, that very accurately predict the progression of inflammation and crisis hazard in patients with progressing ARDS. The second is the neutrophil/lymphocyte ratio (NLR), which is the ratio of the absolute number of neutrophils to the lymphocyte count [37]. This variable is used to predict the severity of inflammation and the probability of the adverse clinical course of the disease initially when it is higher than 3 [38, 39]. This ratio is significantly and directly correlated with lung lesions seen in multislice computed tomography (MSCT) scans ($r=0.823$; $p<0.001$) [40]. Moreover, an increase in NLR by one unit is associated with an 8% increase in the risk of death in patients with COVID-19. The cut-off level is five units [41]. Interestingly, NLR>10 at admission insignificantly increases the risk of invasive ventilation and death. However, by day 7 of the treatment, the same ratio predicts a 3.3-fold increase in the need for invasive ventilation ($p=0.008$) and an 11-fold increase in the risk of death ($p<0.0001$) [42]. The lymphocyte-to-C-reactive protein ratio (LCR) is the second variable, which is easy to use to estimate the severity of inflammation, the course of the disease and the prognosis for patients with COVID-19. It is a ratio of lymphocyte count (in thousands) to the CRB level [43]. Unlike NLR, the higher LCR, the better, and vice versa. LCR >100 by day 7 of hospital stay within COVID-19 lowers the probability of poor prognosis by 80% ($p=0.001$) [42].

Early (proactive) anti-inflammatory treatment was not recommended for a long time. As a result, pulmonary lesions rapidly progressed, sometimes even in younger patients with a seemingly favorable onset of the disease. In these cases, the monitoring of patients (persistent fever, dyspnea, severe asthenia), estimation of lymphocyte count, NLR, LCR, and CRB levels are essential to make timely decisions on the intensification of treatment. Any delay can lead to a deterioration of the prognosis for patients. The MSCT pattern of the lungs is often time lagged compared to the inflammation markers.

The attempt of anti-inflammatory treatment with IL-6 inhibitors (tocilizumab or sarilumab) is late in most cases and made in patients already on ventilation, i.e., it is more a "therapy of despair". Such treatment has been included in the interim guidelines of the Ministry of Healthcare of the Russian Federation [44]. Retrospective studies have shown that tocilizumab effectively reduces the duration of vasopressor support and does not decrease the time to the normalization of the COVID-19 patients' clinical status [45]. In other cases, a reduction in the time to the clinical improvement of ventilated patients with COVID-19 was reported, rather than those not on ventilation. There was also a decrease in mortality, but only in the most severe patients [46]. In a thorough study conducted at Yale University, the use of tocilizumab was associated with a 45% decrease in the risk of death and improvement in the clinical status of patients with COVID-19. However, it increased the risk of superinfections (hospital-acquired pneumonia) from 26% to 54% ($p<0.001$) [47].

The association between the use of tocilizumab and the development of mycosis [48] and its inefficacy in diabetes mellitus and hyperglycemia [49] were described. However, relatively small randomized clinical trials have not yet confirmed the beneficial effect of anti-cytokine therapy on the prognosis for patients with severe COVID-19. At the end of July, the first large-scale randomized trial COVACTA, including 450 patients with COVID-19, was completed. Unfortunately, tocilizumab was shown to influence the prognosis for patients and the need for ventilation, although it brought some decrease in the time of hospital stays of patients with COVID-19 [50]. Moreover, patients with moderate COVID-19 who received sarilumab tended to deteriorate [51]. Nevertheless, the trials of these agents are still underway. In particular, the REMDACTA protocol studies the combination of antiviral remdesivir and tocilizumab [52]. The MARIPOSA [53] and EMPACTA [54] trials examine the possibility of using tocilizumab in addition to the standard therapy of coronavirus-associated pneumonia.

In the absence of IL-6 antagonists recommended by the Russian Ministry of Healthcare for use in critical patients, we had to use the pulse therapy with high-dose intravenous GCs, which allowed interrupting the progression of inflammation, preventing the cytokine storm, reducing the need for mechanical ventilation, and achieving the stabilization of the clinical status of patients [55]. It has become clear that we were right, and steroid therapy of patients with COVID-19, in the absence of other possibilities, is entirely possible. In the large randomized RECOVERY trials, including more than 6,400 patients with COVID-19, dexamethasone (6 mg/day for ten days) significantly reduced the risk of death by 17%. However, excellent results were achieved in patients on invasive mechanical ventilation. The risk of death increased by 19% in mild patients [56]. In other words, the results were the same as with sarilumab. In another study, the pulse therapy with intravenous (IV) methylprednisolone 250 mg in the first 24 hours followed by 80 mg for another five days in combination with intravenous tocilizumab 8 mg/kg significantly reduced the risk of mechanical ventilation in 43% of patients and the risk of death by 65% [57]. Despite the high efficacy, the GC therapy was accompanied by a clear trend of an increased risk of pulmonary embolism (21% vs. 11%, p=0.059). In our study WAYFARER, similar to other trials, GCs showed a significant increase in NLR, as well as a good clinical effect and a decrease in CRB levels [42]. As a result, the prothrombotic action of GCs caused the risk of thrombotic and thromboembolic complications, which could require more intense anticoagulant therapy and delayed recovery [55].

The lack of effect even of the aggressive anti-inflammatory and anti-cytokine therapy in severe patients with mysterious pneumonia in COVID-19 raised the question of possible additional mechanisms of the onset and progression. The increase in the levels of pro-inflammatory cytokines and chemokines turned out to be several-fold lower in patients with COVID-19 than in patients with ARDS of other origins [58]. Thus, despite the commonly used term "cytokine storm", inflammation is not the only factor in disease severity. The rapid onset of coagulopathy and increased thrombosis (brown line in Figure 1) is the third unique mechanism of the onset and progression of COVID-19 (besides viral infection and autoimmune inflammation). The early Chinese trials showed that the D-dimer levels in multivariate analyzes determined the adverse course of the disease, increased risk of mechanical ventilation, and higher mortality [59–61]. The incidence of massive venous thrombosis and thromboembolism in COVID-19 ranges from 20 to 35%, which allowed considering this viral disease as a prothrombotic condition [62–65]. In this case, NLR may be of great use as its elevation above 5.7 units increases the risk of massive thromboembolism by 10.8 times, and the risk of death [66]. A significant direct positive correlation was identified in the WAYFARER study between changes in NLR and D-dimer levels and the risk of venous thrombosis and thromboembolism [55].

A distinguishing characteristic of the new coronavirus disease is the increased risk of microthrombosis of small pulmonary vessels found in about 70–80% of patients with COVID-19 and severe pneumonia [67–69]. It should be kept in mind that the more severe the condition, the higher the severity of vascular damage and coagulopathy. However, such changes are identified from the earliest stages of the disease [70, 71]. Simultaneously, gas exchange is disrupted even more, and permanent ARDS rapidly progresses within 1–2 days [63, 72]. Multiple thrombosis foci of small pulmonary vessels are found in autopsies that prevent oxygen diffusion from the alveoli into the blood [10, 12]. Pulmonary changes are obviously considered as autoimmune lesions of alveoli (diffuse dilation, filling with exudate and desquamated epithelial cells) combined with the involvement of pulmonary micro vessels (damaged endothelium and multiple clots) [73]. For patients who are put on ventilation, however, the efficacy is still not guaranteed in this case since the pulmonary damage should be treated not as viral pneumonia but as an autoimmune pneumonitis with the total lesion of both pulmonary tissue (drowning alveoli) and vessels [74, 75].

The presence of coagulopathy from the early stages of the disease suggests that COVID-19 is a prothrombotic condition requiring intense anticoagulant therapy in almost all patients, which was applied in the Lomonosov University Clinic from the first day of treatment of the new coronavirus disease (our recommendations). There are different expert opinions on whether coagulopathy in COVID-19 is a variant of disseminated/septic intravascular coagulation syndrome (DIC/SIC) [76–78]. However, it is evident that prothrombotic status largely determines the prognosis for patients with COVID-19 [79, 80]. Autoimmune inflammation of vascular endothelium of various organs (kidneys, intestine, heart, and even prostate) with typical microthrombosis has been shown. There is clear evidence that anticoagulant therapy significantly improves the prognosis for patients with COVID-19 [62, 64]. Moreover, there is evidence that the more aggressive anticoagulant treatment, the better the prognosis for patients with COVID-19 [81]. Thus, mandatory anticoagulant therapy is the backbone of the management of patients with COVID-19 from the early stages of the disease, and its intensity should be

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increased as the disease progresses [82, 83]. The risk of bleeding should naturally be carefully controlled during active anticoagulant therapy [84].

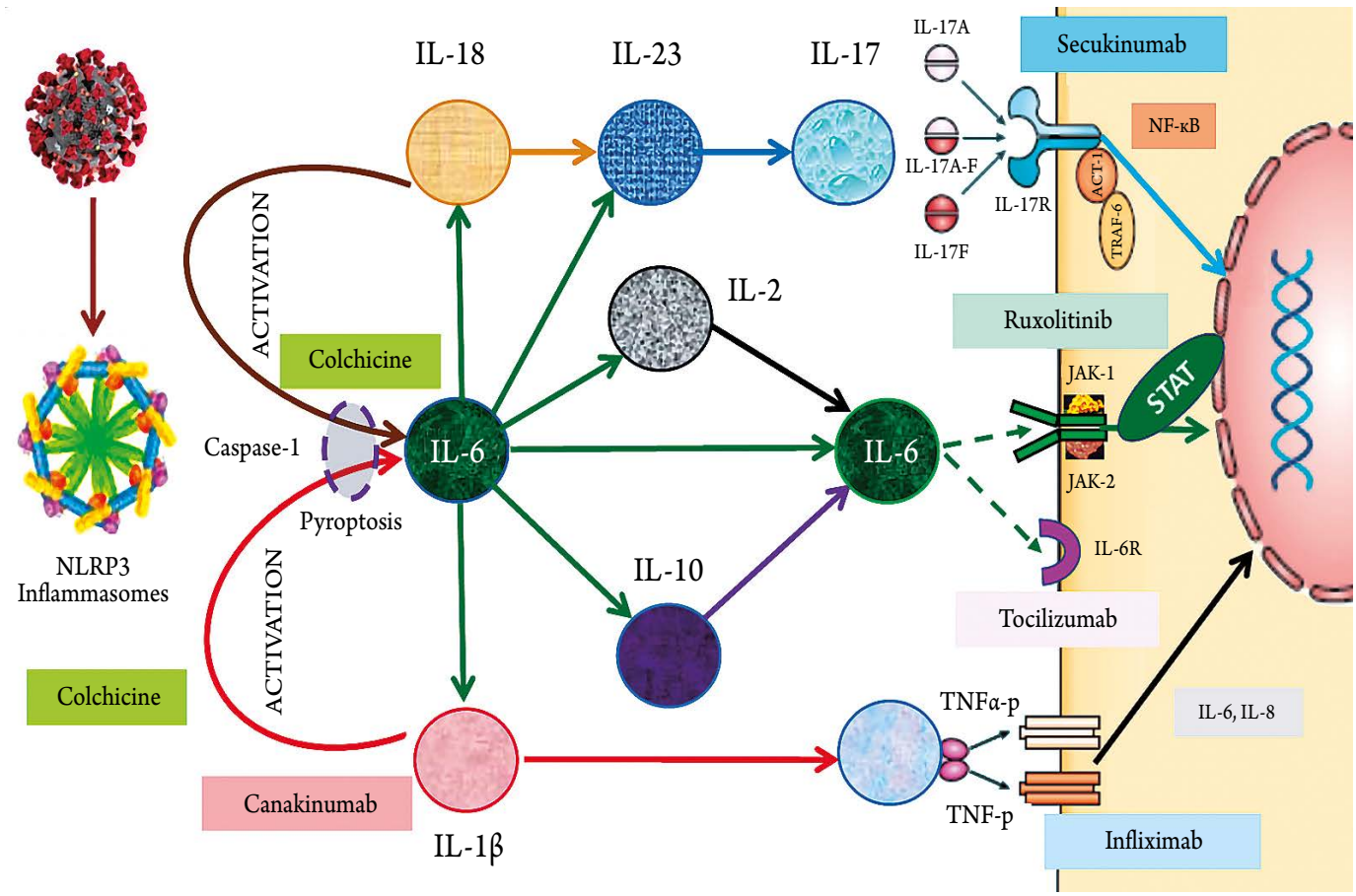
The need for active anticoagulant therapy in patients with COVID-19 at all stages of the disease is beyond doubt and was shown to be effective [83, 85]. However, it is only a correction of the effects associated with autoimmune inflammation. There is little hope for success without affecting the pulmonary damages root cause in COVID-19 [86]. Control of systemic inflammation should therefore be the cornerstone of the management of COVID-19, particularly its severe forms. Given that active anticoagulant therapy with low-molecular-weight heparins (LMWHs) was used in ALL of our patients, the subject of our study was the choice of proactive specific anti-inflammatory therapy.

The main factors stimulating autoimmune inflammatory responses in viral infectious diseases are shown in Figure 3.

As can be seen, when SARS-CoV-2 enters the bronchi and alveoli, the inflammasomes and the multiprotein complex are activated. The latter promotes pyroptosis, i.e., programmable cell death, through the activation of the enzyme capapase-1 [87]. It is a mechanism of cell protection from the infection attack, which is accompanied by the desquamation of alveolar epithelial cells [88]. The cell membrane is destroyed, and pro-inflammatory cytokines IL-1β and IL-18 are secreted in this case [89]. One of the main consequences is the increased production of IL-6 in response to the ongoing viremia [90]. IL-6 is a crucial promoter of autoimmune protection transferring into inflammation and, in its excessive secretion, into a cytokine storm exacerbating the course of coronavirus-associated pneumonia [91]. This process in COVID-19 involves activation of a sufficient number of various chemokines and cytokines capable of supporting the state of autoimmune inflammation and elevated clotting, including IL-17 [92] and tumor necrosis factor-alpha (TNFα) [93].

This concept suggests various points of application of the drug-induced effects that can interrupt the progress of inflammation and clotting, which theoretically can be useful in the treatment of COVID-19 (Figure 3). Specific anti-interleukin IL-1β antibodies can be used to try to reduce the production of IL-6 [94]. For example, the drug with such an effect, canakinumab, significantly reduced death risk in patients after myocardial infarction by reducing the severity of autoimmune inflammation [95]. The most popular method for controlling the cytokine storm turned out to be anti-IL-6 receptor antibodies

Figure 3. Autoimmune inflammation, pro-inflammatory factors, and possible points of actions of potential drugs in COVID–19



(tocilizumab and sarilumab), which were considered from the very beginning of the epidemic. Unfortunately, this method can be used as the last resort in the fight against cytokine storm in patients who are already put on ventilation [96], as discussed above. The use of janus kinases (JAK-1, JAK-2) blockers is an alternate. The effect of the main cytokines, including IL-6, is transmitted to cells through janus kinases. Here, we are talking about ruxolitinib, which has already been studied in small yet promising trials in patients with COVID-19 [97]. IL-17 can also be an important element in the autoimmune response that stimulates a pro-inflammatory state and tendency to thrombosis when overactivated [98–100]. Italian researchers made an interesting observation that the course of COVID-19 in patients routinely treated for psoriasis with secukinumab was extremely mild [101]. Given this observation, the use of monoclonal antibodies blocking IL-17 (e.g., secukinumab) in the treatment of COVID-19 also seems promising [92, 102]. The use of biological anti-immune drugs in the treatment of viral infections, including COVID 19, seems to be an exploratory option, since it is impossible to predict and even justify the efficacy of anti-cytokine agents [103, 104]. Moreover, aggressive anti-cytokine therapy can lead to the onset of superinfections, which may outweigh the benefit of anti-inflammatory therapy in patients with COVID-19 [105].

The use of colchicine, a well-known drug for treating acute gout flares, is of great interest here [106]. Attention to colchicine in recent years has continued, since its efficacy was shown in patients with acute myocardial infarction [107]. The main anti-inflammatory effects of colchicine are associated with the inhibition of inflammasomes, the reduction of pyroptosis, and the decreased activation of cytokines [108]. Moreover, colchicine bound to the intracellular protein tubulin, which forms microtubules, can disrupt the entrance of viruses into the cell nuclei and subsequent replication, thus reducing the viral load [109]. The first completed randomized trial of colchicine in patients with COVID-19, GRECCO-19, found that it might be a potential cure for this disease [110]. The use of colchicine shortened the time to the normalization of the clinical condition. However, there was no significant reduction of CRB as a marker of inflammation. Colchicine is one of the most studied drugs used to treat COVID-19 (randomized prospective protocols COLCORONA [111] including 6,000 patients and COLCOVID [112] with 2,500 patients).

We also conducted a prospective randomized trial COLORITE [113] of early proactive anti-inflammatory therapy in patients with COVID-19, which is presented in Figure 4.

Patients with confirmed COVID-19 and two other signs: fever >37.5°C and persistent cough, dyspnea with respiratory rate >24 breaths per minute or blood oxygen saturation <93%, and CRB level >60 mg/L, were randomized to four groups: control (without specific anti-inflammatory therapy); colchicine 1 mg on day 1 followed by 0.5 mg/day; ruxolitinib (Jakavi®) 5 mg bid; secukinumab (Cosentyx®) 300 mg subcutaneously, single dose. The primary endpoint was the SHOKS-COVID score, which had been used earlier in the WAYFARER trial of GCs [55]. The secondary endpoints were changes in the clinical condition, components of the primary endpoint, CRB and D-dimer in the first instance, assessment of the quality of life using the visual analog scale (VAS) and the validated EQ-5D questionnaire, and duration of hospital stays, need for mechanical ventilation, and prognosis for days 14 and 45 of treatment.

The background therapy included high doses of anti-coagulants (LMWHs), the combination of bromhexine and spironolactone, and antibiotics as appropriate, in all patients. As a priority, we are going to finalize this work as soon as practicable.

In the following section of this paper, we will present a number of case studies including clinical observations, which demonstrate the feasibility of proactive anti-inflammatory therapy interventions.

Patient I., 53 years old, a positive test for SARS-CoV-2 (polymerase chain reaction (PCR)), was treated for bilateral coronavirus-associated pneumonia in a Moscow clinic for 21 days (without specific anti-inflammatory therapy) and was discharged after clinical improvement with normal body temperature, minimal dyspnea, grade 1 pulmonary damage (MSCT, Guidelines of the Ministry of Healthcare of the Russian Federation), normal lymphocyte count and CRB level (1.0 mg/L). Three days after discharge, the patient's body temperature raised again, dyspnea increased, and plinavir/ritonavir, azithromycin, paracetamol, and bacterial lysates were recommended. The patient did not improve and was hospitalized in the Lomonosov University Clinic on May 6 (four days after the onset of their symptoms). A PCR test for SARS-CoV-2 RNA was negative.

At admission: subfebrile fever 37.9°C, moderate dyspnea (18 breaths per minute); blood oxygen saturation 98%; lymphocytes at lower limit of normal 1.01×109/L; NLR 3.8; erythrocyte sedimentation rate (ESR) 21 mm/h; IL-6 11.9 pg/mL; CRB 54.8 mg/L, and D-dimer 0.72 μg/mL. There was a small pulmonary lesion on an MSCT (Figure 5) scan, mainly on the left, 6.1% in volume, but with consolidations. It was

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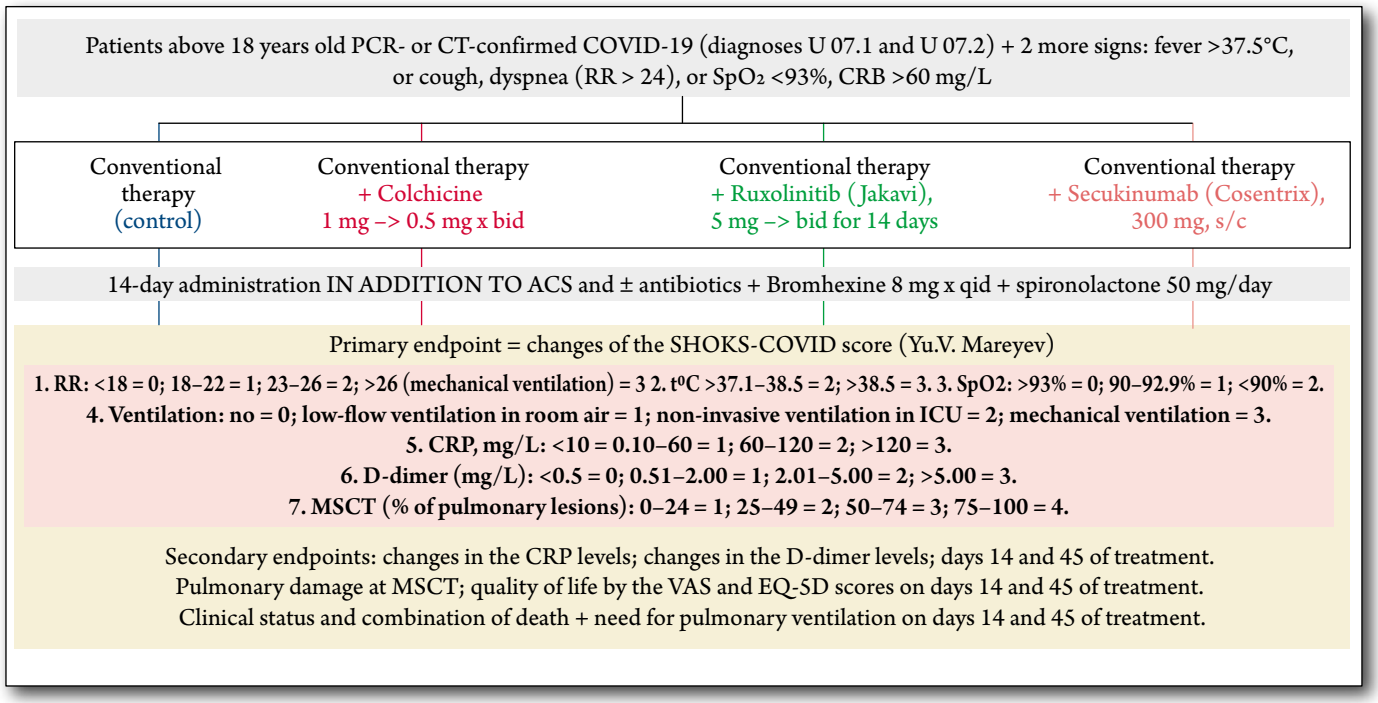
Figure 4. Colchicine versus ruxolitinib and secukinumab in thw open-label prospective randomized trial in patients with COVID-19 (COLORIT)



PCR, polymerase chain reaction; CT, computed tomography; ICU, intensive care unit; SHOKS-COVID, COVID-19 clinical status scale; RR, respiratory rate; CRP, C-reactive protein; MSCT, multislice computed tomography; VAS, visual analog scale.

estimated as a resolution to long-term inflammation. Despite a moderate increase in pro-inflammatory factors (IL-6 and CRB), the relatively calm clinical course and minimal pulmonary damage with a negative PCR test for COVID-19 did not prompt us to start anti-inflammatory treatment. Anticoagulant therapy (enoxaparine 0.6 mL od, subcutaneously), antibiotic (moxifloxacin 400 mg/day), and a combination of bromhexine 8 mg qid and spironolactone 50 mg/day were prescribed. The disease progressed rapidly. Two days later, on May 8, the body temperature was subfebrile (37.8°C), dyspnea increased to 22 breaths per minute, blood oxygen saturation decreased to 96% in the prone position, ESR increased to 56 mm/hour, lymphocyte count and NLR changed little. However, IL-6 levels increased to 36.3 pg/mL (5-fold higher than normal), and CRB increased sharply to 214.8 mg/dL (43-fold higher than normal). D-dimer also increased to 1.16 μg/mL. The volume of pulmonary damage increased to 44% (both lungs were involved, mainly new ground-glass nodules) within two days. This example illustrates how easy it is to make a mistake and underestimate the severity of patients with COVID-19. This patient had a second-type response to the infection in the form of increased cytokine release syndrome (green line Figure 2). Thus, colchicine 1 mg was started on day one, followed by 0.5 mg/day. The dose of enoxaparin was increased to 0.6 mL bid subcutaneously. The patient recovered gradually, and observable improvement was achieved two weeks later: body temperature 36.5°C, blood oxygen saturation 98%, RR 16 breaths per minute, IL-6 1.5 pg/mL, CRB 2.42 mg/dL, D-dimer 0.2 μg/mL, and the volume of ground-glass nodules decreased from 44% to 7%. It is worth noting that such inflammatory response transforms rapidly into massive pulmonary damage in the second-type immune response. Timely specific anti-inflammatory therapy also enables recovery from coronavirus-associated pneumonia relatively quickly (within 1–2 weeks).

Patient S., 69 years old, body mass index 30.7 kg / m^2, with PCR-confirmed COVID-19 and bilateral multisegmental pneumonia, was admitted to the clinic on day 12 of the disease with persistent fever (39°C maximum, 37.5°C at admission), dyspnea with RR 20 breaths per minute, persistent dry cough, and reduced blood oxygen saturation up to 96%. Comorbidities: hypertension hypertensive heart disease grade 2, aortic atherosclerosis, brachiocephalic arteries, dyslipidemia. Losartan 50 mg bid, bisoprolol 2.5 mg od, rosuvastatin 10 mg od were continued to control BP and lipid levels.

Blood tests showed a significant decrease in lymphocyte count 0.5×109/L, NLR elevated to 23 (!); IL-6 52.9 pg/mL; CRB 159.5 mg/dL; D-dimer 0.84 μg/mL. MSCT revealed bilateral pulmonary damage, a total volume of 30%, mainly as ground-glass nodules (Figure 6).

The patient's condition was considered a severe autoimmune inflammation requiring emergency intervention. This is the third type of immune response to viral infection in the form of decreased cytokine release syndrome (red line in Figure 2) and long-term persistent course of difficult-to-treat viral infectious disease.

Bromhexine 8 mg qid, spironolactone 50 mg/day, enoxaparin 0.8 mL od subcutaneously, ceftriaxone 1000 mg bid. After signing an informed consent form, the patient received ruxolitinib (Jakavi®) 5 mg bid on the first day of the hospital stay (small doses are used to avoid the reaction of hemopoiesis reduction).

The patient's clinical state improved relatively quickly. Two days later, body temperature normalized, RR decreased to 18 breaths per minute, blood oxygen saturation increased to 98%, CRB decreased to 98.3 mg/dL on day two of the treatment, 49.4 mg/dL on day hour, and 6.76 mg/dL by the end of week one. The lymphocyte count increased to the lower limit of normal 1.1×109/L, and NLR decreased sharply to 2.7, and D-dimer decreased to 0.55 μg/mL. Nevertheless, the area of the pulmonary damage almost did not decrease (Figure 6).

Six days later, the patient's condition normalized: body temperature 35.5°C, no dyspnea (RR 16 breaths per minute) and cough, blood oxygen saturation 99%, lymphocyte count increased to normal 1.63×109/L, and NLR was 2.0. D-dimer normalized to 0.25 μg/mL as inflammation decreased and IL-6 reduced to 2.09 pg/mL, and CRB to 1.08 mg/dL. There were still ground-glass nodules in MSCT, mainly in the right lung, with a total volume of 20%. It is typical of the third-type immune response to viral infection when the onset of pneumonia is gradual and reaches the maximum by weeks 2 to 3. In such cases, even active, effective, and timely anti-inflammatory therapy, e.g., ruxolitinib (Jakavi®), does not eliminate pulmonary fibrosis quickly. It has been shown that not all symptoms disappeared in the acute period of the disease and were often observed within a month after hospital treatment [114].

Patient K., 31 years old, with PCR-confirmed viral pneumonia and concomitant chronic obstructive pulmonary disease and bronchial asthma, was admitted on day 8 of the disease with complaints of fever (37.6°C), dyspnea (RR 20 breaths per minute), feeling of chest congestion during physical activity, headache, dyspnea mainly at night, low-productive cough with scanty light sputum with brownish inclusions, loss of taste and smell, nausea, weakness. The patient used beclomethasone 2 breaths bid and occasionally ipratropium bromide + phenoterol for bronchial asthma since childhood. Due to the suspicion of COVID-19, the patient took imidazolyl ethanamide pentandioic acid and paracetamol on an outpatient basis for seven days. From day four of the disease, hydroxychloroquine 400 mg/day (canceled due to urticaria) and azithromycin (no apparent beneficial effect) were prescribed.

Figure 5. MSCT scan of the lungs of 53-year-old patient I. with COVID-19 and bilateral pneumonia (see details in the text)

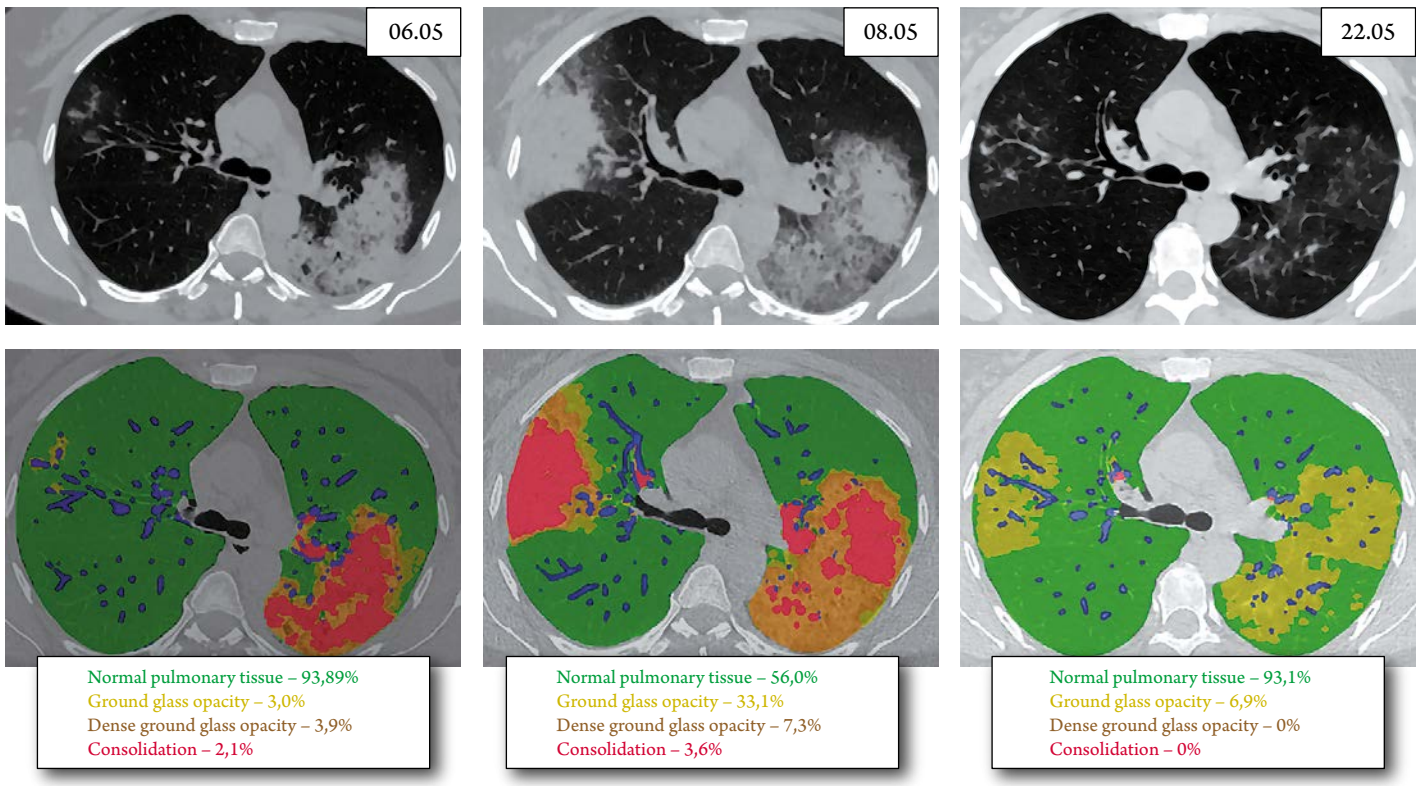


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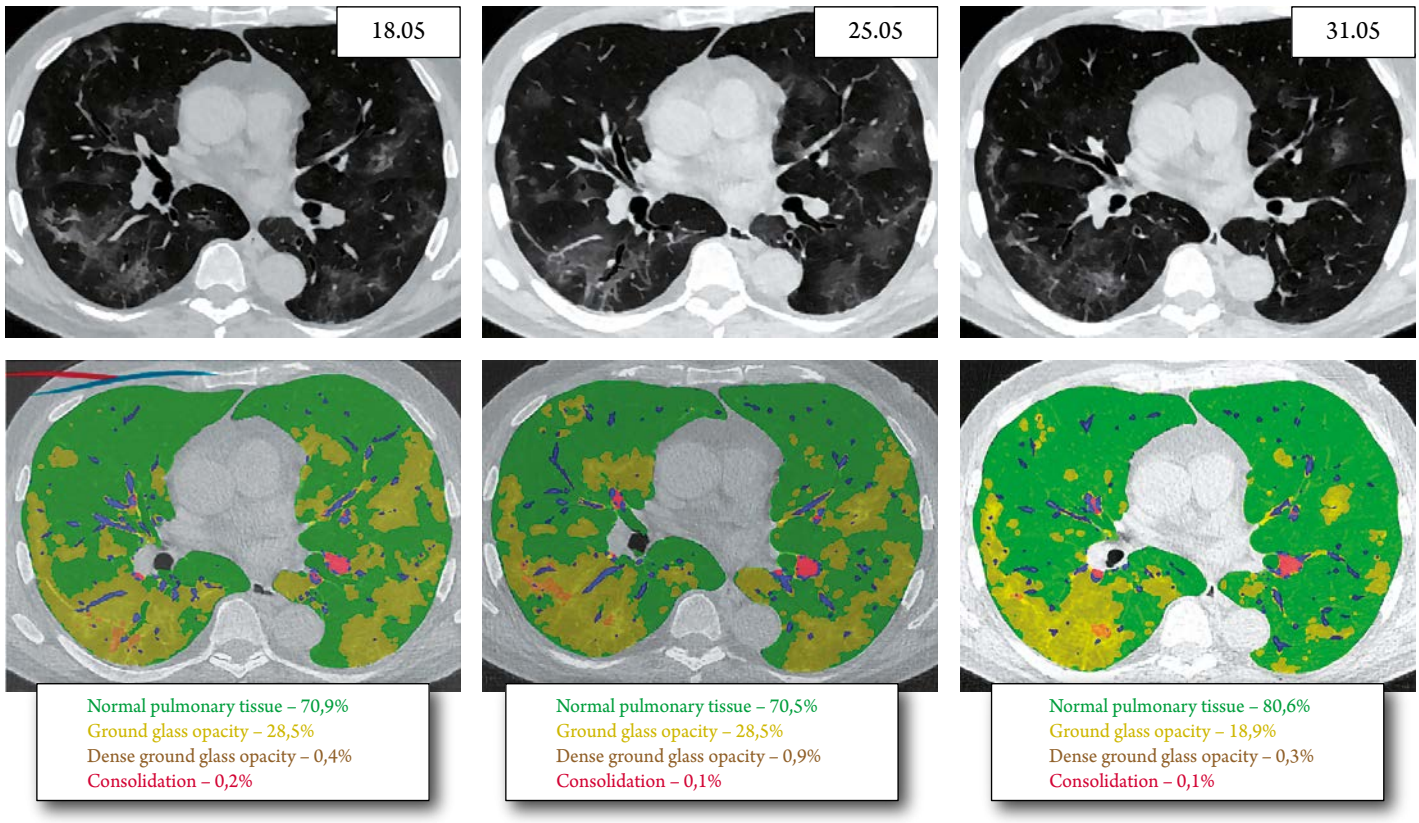
Figure 6. MSCT scan of the lungs of 69-year-old patient I. with COVID-19 and bilateral pneumonia (see details in the text)

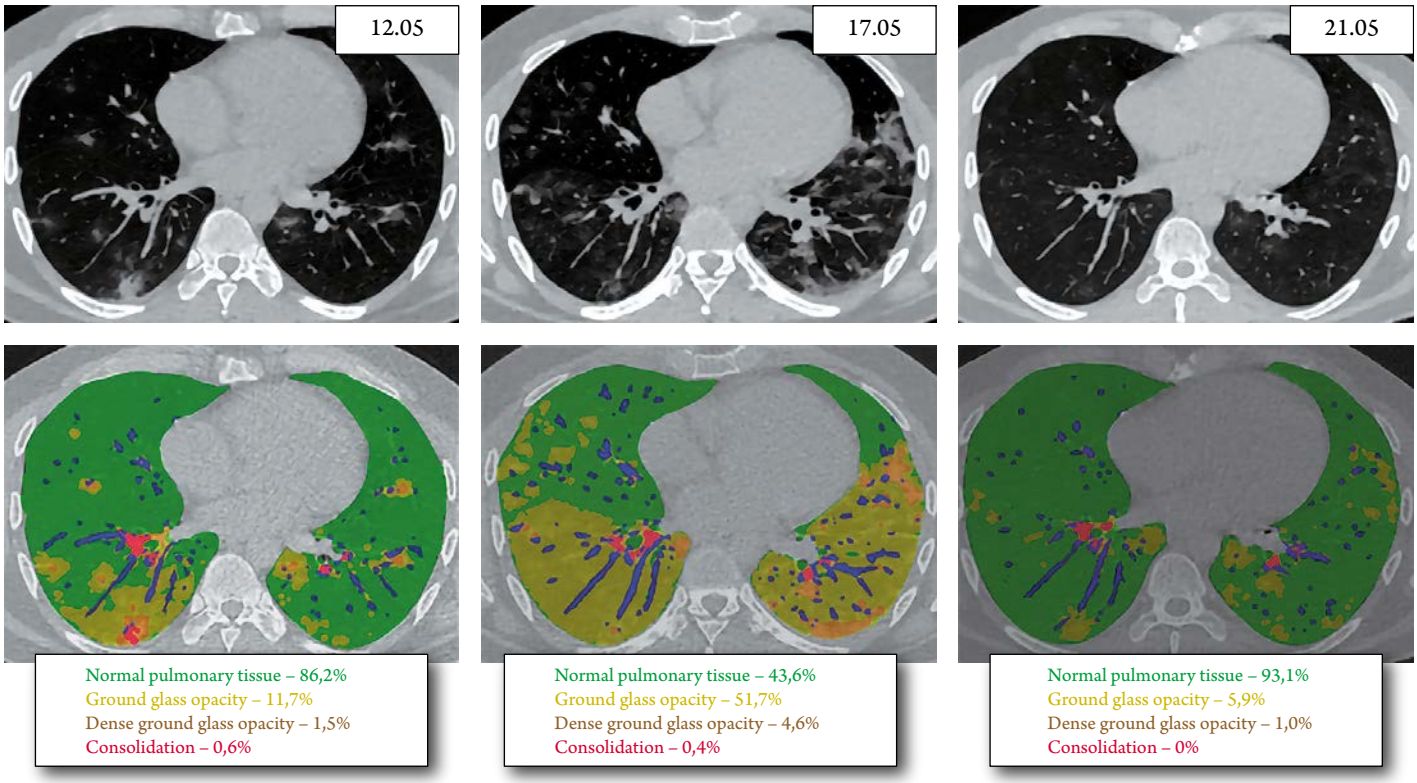


On admission, a significant reduction in blood oxygen saturation to 93% was considered to be due more to bronchial asthma than viral pneumonia. On 12.05.2020, an MSCT (Figure 7) scan showed the area of lesion was only 14% in the form of mild ground-glass opacities. Lymphocyte count (2.03×109/L), NLR, and D-dimer level (0.33 μg/mL) were normal. IL-6 was not estimated, and CRB elevated to 69.4 mg/dL combined with a moderate increase in lactate level to 3.91 mmol/L which could be associated with acute exacerbation of bronchial asthma. Moreover, the thrombocyte count was decreased (135×109/L). Bromhexine 8 mg qid, dual antibiotic therapy with ceftriaxone 1000 mg bid and amoxicillin 1000 mg + clavulanic acid 1000 mg intravenously tid, and anticoagulant enoxaparin 0.4 mL od subcutaneously were added.

Despite the therapy, the patient's condition did not improve significantly, although cough and chest congestion disappeared, subfebrile temperature, and dyspnea with blood oxygen saturation of 93–94% yet persisted. Five days later (day 13 of the disease), IL-6 increased to 46.2 pg/mL (6.6-fold higher than normal) and CRB to 201.1 mg/dL (40-fold higher than normal) with D-dimer remaining at a normal level of 0.17 μg/mL, which allowed us to assume the intermediate (transition from the second to the third) type of autoimmune response and cytokine release syndrome (Figure 2). The pulmonary lesion increased very rapidly in the form of disseminated ground-glass opacities (MSCT) in both lungs from 14 to 57% within five days. When informed consent was received, anti-IL-17 monoclonal antibody secukinumab (Cosentrix®) 300 mg was injected subcutaneously.

The effect was observed by day 3 of treatment as body temperature normalized, the patient's sense of smell returned, and CRB decreased to 33.8 mg/dL (6-fold within three days). Day 5 of the treatment: body temperature 36.5°C; RR 16 breaths per minute; blood oxygen saturation 99%; lymphocyte count 2.41×109/L; NLR 1.1; platelet count increased from 135 to 309×109/L; IL-6 2.23 pg/mL; CRB 11.7 mg/dL; D-dimer 0.53 μg/mL. Rapid reduction of the MSCT pulmonary damage area from 56 to 6% (also within five days). It should be noted that the dose of the LMWH was low because the patient had a low platelet count. It may be partly associated with a borderline level of D-dimer by the end of treatment. Therefore, oral anticoagulants (rivaroxaban 10 mg/day) were recommended at discharge. Otherwise, this is one more vivid example of the rapid effect of anti-inflammatory therapy with secukinumab in a young patient with the second-type autoimmune response despite concomitant bronchial asthma. The delay of the anti-inflammatory treatment was not crucial due to the patient's young age and responsive immune system.

Figure 7. MSCT scan of the lungs of 31-year-old patient K. with COVID-19, bilateral pneumonia, and bronchial asthma (see details in the text)



Patient A., 80 years old, was admitted on day 6 of the disease with a positive PCR which indicated COVID-19 and bilateral coronavirus-associated pneumonia. Comorbidities: type-2 diabetes mellitus (compensated with drugs), grade 2 hypertension, chronic (latent) glomerulonephritis, bilateral kidney cysts, stage 5 chronic kidney disease, postoperative hypothyroidism (compensated with drugs), gout, benign prostatic hyperplasia, spondyloarthritis. Therapy for comorbidities included glimepiride 1 mg/day and alogliptin 25 mg/day to control glycemia within 6.0–8.0 mmol/L, losartan 25 mg bid, furosemide (periodically controlled by diuresis) and nebivolol 7.5 mg/day to control BP at 140/80 mmHg; atorvastatin 40 mg od to control cholesterol levels.

The disease onset was acute with an increase in body temperature to 39°C, dyspnea, cough, sore throat, pronounced weakness, complete loss of smell, diarrhea. Outpatient treatment included cefazolin, bromhexine, paracetamol. Despite the therapy, during a few days, the patient complained of deteriorating the condition, worsening of dyspnea, and asthenia. Outpatient MSCT: bilateral polysegmental pneumonia, highly-likely stage 1 coronavirus-associated pneumonia (area of the pulmonary damage less than 25%).

On admission to Lomonosov University Clinic, body temperature was 37.9°C, severe dyspnea (RR 22 breaths per minute); heart rate 100 bpm, BP 140/70 mmHg, blood oxygen saturation 92%. The patient was not able to lay in the prone position due to acute spondyloarthritis. MSCT showed moderate pulmonary damage 28.8%, more on the left with 11% of dense ground-glass nodules (areas of airless parenchyma) (Figure 8), which already corresponds to stage 2 damage (according to the classification of the Russian Ministry of Healthcare). Blood tests: increased leukocyte count 12.3×109/L; relatively low lymphocyte count 1.11×109/L, and very high neutrophil count 10.69×109/L; NLR elevated to 9.6; ESR 38 mm/h. All pro-inflammatory factors were elevated: IL-6 up to 150.6 pg/mL (20-fold), CRB up to 232 mg/dL (46-fold), and ferritin up to 621 μg/L. D-dimer was significantly increased to 2.62 μg/mL (more than 5-fold). Renal failure complicated the situation: creatinine was increased to 344 μmol/L and glomerular filtration rate (GFR) was reduced to 14 mL/min/1.73 m^2 (CKD-EPI). Glucose was slightly increased to 6.8 mmol/L, but there was a risk of lactoacidosis (lactate 7.1 mmol/L).

Symptomatic treatment was initiated: bromhexine 8 mg qid and acetylcysteine, ketoprofen intravenously administered for pain, tizanidine hydrochloride 2 mg/day, and omeprazole. Levofloxacin 500 mg od intravenously administered was ordered as antibacterial therapy. Anticoagulant treatment included enoxaparin 0.6 mL subcutaneously bid. The condition was regarded as severe autoimmune inflammation, which could progress to a cytokine storm (lilac line in Figure 2). After

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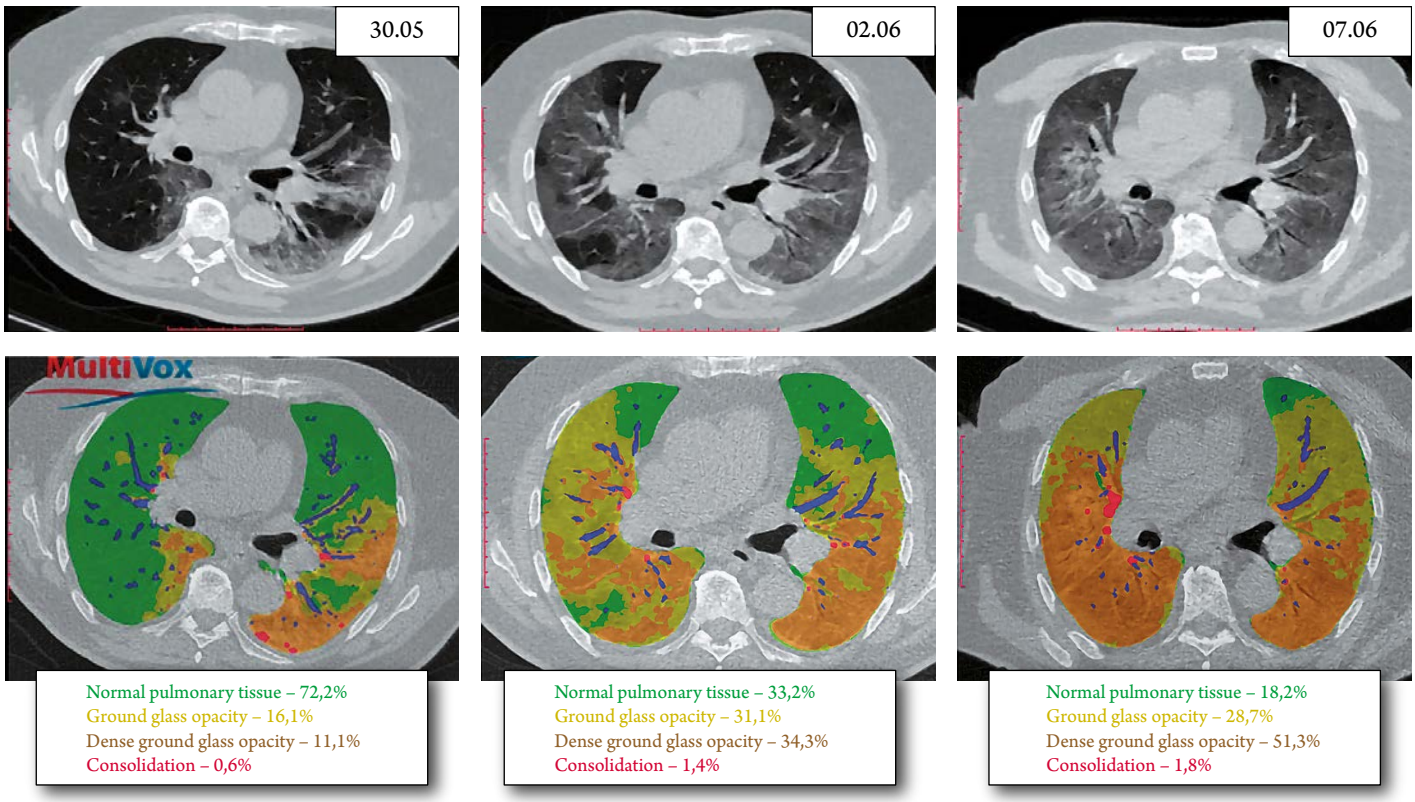
the patient gave his informed consent, treatment with secukinumab (Cosentyx®) 300 mg subcutaneously and oral dexamethasone 8 mg bid was immediately initiated.

Within the next three days, body temperature was not higher 37.2°C; dyspnea and weakness decreased slightly, but blood oxygen saturation remained very low 86% with atmospheric air and 94% with oxygen-enriched air (V 5 L/min). Creatinine levels remained almost the same, but glucose increased to 10.3 mmol/L despite ongoing hypoglycemic therapy. Leukocyte count remained elevated at 12.7×109/L; lymphocyte count decreased more up to 0.41×109/L, NLR increased to 31, and D-dimer was 1.3 μg/mL. IL-6 significantly decreased to 23.5 pg/mL, CRB gradually decreased (by day): 232 mg/dL; 231 mg/dL; 121 mg/dL; 110 mg/dL. Nevertheless, MSCT on 02.06.2020 (day 11 day of the disease) (Figure 8) showed significantly increased lesion of the pulmonary parenchyma, especially in the lower lobes up to 66.8% with dense ground-glass opacities with reduced airiness up to 34.3%, which corresponded to stage 3 lesion (classification of the Russian Ministry of Healthcare).

The board of physicians of Lomonosov University Clinic evaluated the patient's condition as progressive autoimmune inflammation developing into a full-blown cytokine storm unresponsive to anti-IL-17 antibodies and low-dose GCs. It was decided to change the antibiotic therapy (transfer patient to cefaperazone+sulbactam 1000 mg bid) and order emergency pulse therapy with high-dose GCs (methylprednisolone 500 mg – 500 mg – 250 mg – 125 mg intravenously administered in combination with colchicine 1 mg on day one followed by 0.5 mg/day). Taking into account the risk of acidosis, acetazolamide 250 mg bid was added to the therapy. After an endocrinological consultation, it was decided to transfer the patient to insulin. This treatment allowed for a decrease in IL-6 to 11 pg/mL and CRB to 37.2 mg/dL within 5 days (by day 16 of the disease), but the patient's condition worsened: dyspnea and chest congestion increased, blood oxygen saturation remained low (85 to 88% with atmospheric air and 92 to 94% with oxygen-enriched air (V 10 L/min)). Weakness, asthenia progressed. The patient felt depressed and anxious. Thus, hydroxyzine 25 mg at bedtime was ordered. Low lymphocyte count 0.5×10 9/L persisted, leukocyte count increased more up to 20.2×109/L, and NLR increased sharply to 38.4. Blood glucose remained high 10.9 mmol/L and lactate increased moderately 4.2414 mmol/L, creatinine level was high 382 mmol/L and estimated GFR was critically low at 12 mL/min/1.73 m² (CKD-EPI). The relative density of urine was low – 1005; proteinuria 0.5 g/L, glucosuria (+), ketones (+), hematuria 65,9 cell/UL, and increased levels of yeast in urine up to 58.8 kl/UL. D-dimer levels remained elevated up to 1.78 μg/mL. Control MSCT

Figure 8. MSCT scan of the lungs of 80-year-old patient K. with COVID-19, bilateral pneumonia, and type 2 diabetes mellitus, CKD stage 5, hypertension, podagra (see details in the text)



(Figure 8) showed continuing progression of pulmonary damage up to more than 80% bilaterally, and almost airless zones in the form of dense ground-glass lesions involving more than half of the pulmonary parenchyma (stage 4 according to the classification of the Russian Ministry of Healthcare).

Antibiotic therapy was changed one more time, and meropenem 2–3 g/day depending on GFR and metronidazole 500 mg bid were ordered. The next day, breathing became more difficult, tachypnoea increased to 28 breaths per minute with auxiliary muscles involved in the act of respiration and decreased blood oxygen saturation to 88% when breathing with humidified oxygen-enriched air. The patient was transferred to the ICU, where non-invasive ventilation of the lungs was initiated (10 L/min) through a mask. Water-electrolyte disbalance was corrected. Small doses of noradrenaline and symptomatic therapy were used to stabilize hemodynamics. Intensive double anti-inflammatory (dexamethasone and colchicine) and anticoagulant (enoxaparin) therapies continued. The patient's condition remained severe. As the COVID-19 treatment center was closed in the clinic, the patient was transferred to the intensive care department of a city hospital (day 17 of the disease), where he was pronounced dead the next day (day 18 of the disease).

This last case is a typical course of cytokine storm and progressive pulmonary damage in COVID-19, when all efforts cannot achieve efficacy and any therapy, including combined anticoagulant and anti-inflammatory treatment, is ineffective. Of course, age and multiple comorbidities were the aggravating factors in this case and event, then only proactive therapy could give a chance for success and full recovery of the patient. By the time of the active anti-inflammatory treatment (day 7 of the disease), levels of IL-6, CRB and ferritin had already increased multifold, and NLR was as high as 9.6 (normal level less than 3). Moreover, pneumonia rapidly progressed despite intense anti-inflammatory and anticoagulant therapy. Although IL-6 and CRB decreased during the treatment with high-dose GCs + secukinumab + colchicine, it was changes in NLR (9.6 at admission, 31 in 5 days, and 38.4 in other five days) that were most closely correlated with the progression of coronavirus-associated pneumonia and indicative of adverse prognosis. However, the main lesson of this case is the assumption that proactive anti-inflammatory therapy (such as colchicine), especially in high-risk patients, should begin as early as possible together with antiviral treatment (possibly even before hospitalization).

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REFERENCES

1. Pericàs JM, Hernandez-Meneses M, Sheahan TP, Quintana E, Ambrosioni J, Sandoval E et al. COVID-19: from epidemiology to treatment. European Heart Journal. 2020;41(22):2092–112. DOI: 10.1093/eurheartj/ehaa462
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239. DOI: 10.1001/jama.2020.2648
3. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708–20. DOI: 10.1056/NEJMoa2002032
4. Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. International Journal of Infectious Diseases. 2020;94:81–7. DOI: 10.1016/j.ijid.2020.03.040
5. Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. European Heart Journal. 2020;41(22):2058–66. DOI: 10.1093/eurheartj/ehaa433
6. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tré G, Belmans L et al. The Effects of ARBs, ACEis, and Statins on Clinical Outcomes of COVID-19 Infection Among Nursing Home Residents. Journal of the American Medical Directors Association. 2020;21(7):909-914.e2. DOI: 10.1016/j.jamda.2020.06.018
7. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. Journal of Diabetes Science and Technology. 2020;14(4):813–21. DOI: 10.1177/1932296820924469
8. Mareev V.Yu., Orlova Ya.A., Pavlikova E.P., Matskeplishvili S.T., Akopyan Zh.A., Plisyk A.G. et al. Combination therapy at an early stage of the novel coronavirus infection (COVID-19). Case series and design of the clinical trial "BromhexIne and Spironolactone for CoronavirUs Infection requiring hospiTalization (BISCUIT)". Kardiologiia. 2020;60(8):4–15. [Russian: Мареев В.Ю., Орлова Я.А., Павликова Е.П., Мацкеплишвили С.Т., Акопян Ж.А., Плисюк А.Г. и др. Возможности комбинированной терапии на раннем этапе течения новой коронавирусной инфекции (COVID-19). Разбор клинических случаев и дизайн исследования: Бромгексин И Спиронолактон для лечения КоронаВирусной Инфекции, Требующей госпитализации (БИСКВИТ). Кардиология. 2020;60(8):4–15]. DOI: 10.18087/cardio.2020.8.n1307
9. Muus C, Luecken MD, Eraslan G, Waghray A, Heimberg G, Sikkema L et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. Bioinformatics. 2020. Av. at: http://biorxiv.org/lookup/doi/10.1101/2020.04.19.049254.
10. Zayratyants O.V., Samsonova M.V., Mikhaleva L.M., Chernyaev A.L., Mishnev O.D., Krupnov N.M. et al. Pathological anatomy of COVID-19: Atlas. - M.: GBU "NIIOZMM DZM"; 2020. - 140p. [Russian: Зайратьянц О.В., Самсонова М.В., Михалева Л.М., Черняев А.Л., Мишнев О.Д., Крупнов Н.М. и др. Патологическая анатомия COVID-19: Атлас. - М.: ГБУ «НИИОЗММ ДЗМ», 2020. – 140с.]. ISBN 978-5-907251-57-1

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С осторожностью: стеноз аортального или митрального клапана; гипертрофическая обструктивная кардиомиопатия; синдром слабости синусового узла (выраженная тахикардия, брадикардия); одновременное применение с ингибиторами или индукторами изофермента CYP3A4; ангионевротический отек в анамнезе; гипонатриемия; одновременное применение с препаратами лития; гиперкалиемия; гиповолемия (в том числе вследствие диареи, рвоты или одновременного применения диуретиков), а также у пациентов, соблюдающих диету с ограничением потребления поваренной соли; почечная недостаточность легкой и умеренной степени тяжести (КК 20-60 мл/мин); первичный гиперальдостеронизм; вазоренальная гипертензия (двусторонний стеноз почечных артерий или стеноз артерии единственной почки); прочие состояния, сопровождающиеся активацией ренин-ангинотензин-альдостероновой системы; одновременное применение с ингибиторами АПФ или препаратами, содержащими алискирен; хроническая сердечная недостаточность (ХСН) (**III-IV** функциональный класс по классификации NYHA); хронические формы ишемической болезни сердца (ИБС); артериальная гипотензия; ишемические цереброваскулярные заболевания; печеночная недостаточность легкой и умеренной степени тяжести (менее 9 баллов по шкале Чайлд-Пью); пожилой возраст (старше 65 лет); применение у пациентов негроидной расы.

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Побочное действие: Наиболее частыми нежелательными реакциями при применении препарата Аттенто® являются периферические отеки (11,3%), головная боль (5,3%) и головокружение (4,5%).

Подробная информация содержится в инструкции по медицинскому применению лекарственного препарата Аттенто® ЛП - 003818-191219.

* Олмесартан продемонстрировал способность предотвращать или замедлять темпы прогрессирования поражения органов-мишеней

АД – артериальное давление

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Информация для специалистов здравоохранения. Отпускают по рецепту.

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1. Redon J, Fabia MJ. J Renin Angiotensin Aldosterone Syst. 2009 Sep;10(3):147-56.
2. Chrysant SG et al. Clin Ther.2008 Apr;30 (4):587-604
3. De la Sierra A, Volpe M. J.Hypertens.2013 Mar;31 Suppl 1:S13-7

БЕРЛИН-ХЕМИ МЕНАРИНИ

11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine. 2020;46(6):1294–7. DOI: 10.1007/s00134-020-06028-z
12. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. The Lancet. 2020;396(10247):320–32. DOI: 10.1016/S0140-6736(20)31305-2
13. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2008;246(3):697–722. DOI: 10.1148/radiol.2462070712
14. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M et al. Cytokine release syndrome. Journal for ImmunoTherapy of Cancer. 2018;6(1):56. DOI: 10.1186/s40425-018-0343-9
15. Wang J-Y, Chang S-Y, Huang Y-W, Chang S-C. Serology-positive but minimally symptomatic COVID-19 may still cause lung injury and lung function impairment. The International Journal of Tuberculosis and Lung Disease. 2020;24(6):568–9. DOI: 10.5588/ijtld.20.0197
16. Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. International Journal of Antimicrobial Agents. 2020;55(5):105954. DOI: 10.1016/j.ijantimicag.2020.105954
17. Vernadsky R.Yu., Medvedeva A.A., Garbukov E.Yu., Sinilkin I.G., Bragina O.D., Zelchan R.V. et al. Single-photon emission computed tomography with ^{99m}Tc-1-thio-d-glucose for metabolic breast cancer imaging. Russian Electronic Journal of Radiology. 2019;9(4):82–96. [Russian: Вернадский Р.Ю., Медведева А.А., Гарбуков Е.Ю., Синилкин И.Г., Брагина О.Д., Зельчан Р.В. и др. Метаболическая визуализация рака молочной железы методом однофотонной эмиссионной компьютерной томографии с ^{99m}Tc-1-тио-d-глюкозой. Российский Электронный Журнал Лучевой Диагностики. 2019;9(4):82-96]. DOI: 10.21569/2222-7415-2019-9-4-82-96
18. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine. 2020;8(4):420–2. DOI: 10.1016/S2213-2600(20)30076-X
19. Covid-19 treatment Protocol at MSU Medical center. Av. at: http://www.mc.msu.ru/protokol-mnoc.pdf. 2020. [Russian: Протокол лечения COVID-19 Медицинского центра МГУ. 2020. Доступно на: http://www.mc.msu.ru/protokol-mnoc.pdf]
20. The OpenSAFELY Collaborative, Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. Epidemiology. 2020. [Av. at: http://medrxiv.org/lookup/doi/10.1101/2020.05.06.20092999.] DOI: 10.1101/2020.05.06.20092999.
21. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. European Respiratory Journal. 2020;55(5):2000547. DOI: 10.1183/13993003.00547-2020
22. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. Journal of Clinical Investigation. 2020;130(5):2620–9. DOI: 10.1172/JCI137244
23. Tan L, Kang X, Ji X, Li G, Wang Q, Li Y et al. Validation of Predictors of Disease Severity and Outcomes in COVID-19 Patients: A Descriptive and Retrospective Study. Med. 2020; S2666634020300040. [Epub ahead of print]. DOI: 10.1016/j.medj.2020.05.002
24. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020;20(4):425–34. DOI: 10.1016/S1473-3099(20)30086-4
25. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. European Respiratory Journal. 2020;55(6):2001217. DOI: 10.1183/13993003.01217-2020
26. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052. DOI: 10.1001/jama.2020.6775
27. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. The Lancet. 2020;395(10239):1763–70. DOI: 10.1016/S0140-6736(20)31189-2
28. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Internal Medicine. 2020;e203539. [Epub ahead of print]. DOI: 10.1001/jamainternmed.2020.3539
29. Mangalmurti N, Hunter CA. Cytokine Storms: Understanding COVID-19. Immunity. 2020;53(1):19–25. DOI: 10.1016/j.immuni.2020.06.017
30. Rizzo P, Vieceli Dalla Sega F, Fortini F, Marracino L, Rapezzi C, Ferrari R. COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Basic Research in Cardiology. 2020;115(3):31. DOI: 10.1007/s00395-020-0791-5
31. Mohan V, Tauseen RA. Spontaneous pneumomediastinum in COVID-19. BMJ Case Reports. 2020;13(5):e236519. DOI: 10.1136/bcr-2020-236519
32. Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. The Lancet Infectious Diseases. 2020;20(4):510. DOI: 10.1016/S1473-3099(20)30156-0
33. Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F et al. Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE). Microorganisms. 2020;8(5):695. DOI: 10.3390/microorganisms8050695
34. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. European Journal of Heart Failure. 2020;22(5):911–5. DOI: 10.1002/ejhf.1828
35. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chemical Neuroscience. 2020;11(7):995–8. DOI: 10.1021/acschemneuro.0c00122
36. Wunsch H. Mechanical Ventilation in COVID-19: Interpreting the Current Epidemiology. American Journal of Respiratory and Critical Care Medicine. 2020;202(1):1–4. DOI: 10.1164/rccm.202004-1385ED
37. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of Translational Medicine. 2020;18(1):206. DOI: 10.1186/s12967-020-02374-0
38. Imtiaz F, Shafique K, Mirza S, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. International Archives of Medicine. 2012;5(1):2. DOI: 10.1186/1755-7682-5-2
39. Yang A-P, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. International Immunopharmacology. 2020;84: 106504. [Epub ahead of print]. DOI: 10.1016/j.intimp.2020.106504
40. Zhang Y, Wu W, Du M, Luo W, Hou W, Shi Y et al. Neutrophil-to-Lymphocyte Ratio may Replace Chest Computed Tomography to Reflect the Degree of Lung Injury in Patients with Corona Virus Disease 2019 (COVID-19). Av. at: https://www.researchsquare.com/article/rs-23201/v1. DOI: 10.21203/rs.3.rs-23201/v1. 2020.
41. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. Journal of Infection. 2020;81(1):e6–12. DOI: 10.1016/j.jinf.2020.04.002
42. Ullah W, Basyal B, Tariq S, Almas T, Saeed R, Roomi S et al. Lymphocyte-to-C-Reactive Protein Ratio: A Novel Predictor of Adverse Outcomes in COVID-19. Journal of Clinical Medicine Research. 2020;12(7):415–22. DOI: 10.14740/jocmr4227

ISSN 0022-9040. Kardiologiia. 2020;60(9). DOI: 10.18087/cardio.2020.9.n1338

43. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Journal of Medical Virology. 2020; [Epub ahead of print]. DOI: 10.1002/jmv.25819
44. Ministry of Health of Russian Federation. Temporary methodical recommendations. Medical rehabilitation for new coronavirus infection (COVID-19). Version 2 (31.07.2020). Av. at: https://стопкоронавирус.рф/ai/doc/461/attach/28052020_Preg_COVID-19_v1.pdf. 2020. [Russian: Министерство Здравоохранения Российской Федерации. Временные методические рекомендации. Медицинская реабилитация при новой коронавирусной инфекции (COVID-19). Версия 2 (31.07.2020). Доступно на: https://стопкоронавирус.рф/ai/doc/461/attach/28052020_Preg_COVID-19_v1.pdf]
45. Kewan T, Covut F, Al–Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID–19: A retrospective cohort study. EClinicalMedicine. 2020;24: 100418. DOI: 10.1016/j.eclinm.2020.100418
46. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. The Lancet Rheumatology. 2020;2(8):e474–84. DOI: 10.1016/S2665-9913(20)30173-9
47. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clinical Infectious Diseases. 2020; ciaa954. [Epub ahead of print]. DOI: 10.1093/cid/ciaa954
48. Antinori S, Bonazzetti C, Gubertini G, Capetti A, Pagani C, Morena V et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmunity Reviews. 2020;19(7):102564. DOI: 10.1016/j.autrev.2020.102564
49. Marfella R, Paolisso P, Sardu C, Bergamaschi L, D'Angelo EC, Barbieri M et al. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes & Metabolism. 2020;S1262363620300823. [Epub ahead of print]. DOI: 10.1016/j.diabet.2020.05.005
50. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. [Интернет] Available at: https://www.roche.com/investors/updates/inv-update-2020-07-29.htm
51. Parodi E, O'Donnell C. Tocilizumab Fails to Help COVID-19 Patients in Italian Study. The Rheumatologist. 2020; [Av. at: https://www.therheumatologist.org/article/tocilizumab-fails-to-help-covid-19-patients-in-italian-study/]
52. Roche HL. A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared with Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia (REMDACTA). ClinicalTrials.gov Identifier: NCT04409262. [Интернет] Available at: https://clinicaltrials.gov/ct2/show/NCT04409262
53. Hoffmann-La Roche. A Phase-II, Open-Label, Randomized, Multicenter Study to Investigate the Pharmacodynamics, Pharmacokinetics, Safety, and Efficacy of 8 mg/kg or 4mg/kg Intravenous Tocilizumab in Patients with Moderate to Severe COVID-19 Pneumonia (MARIPOSA). ClinicalTrials.gov Identifier: NCT04363736. Av. at: https://clinicaltrials.gov/ct2/show/NCT04363736. 2020 г.
54. Genentech, Inc. A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. ClinicalTrials.gov Identifier: NCT04372186. Av. at: https://clinicaltrials.gov/ct2/show/NCT04372186. 2020 г.
55. Mareev V.Yu., Orlova Ya.A., Pavlikova E.P., Matskeplishvili S.T., Krasnova T.N., Malahov P.S. et al. Steroid pulse -therapy in patients with coronAvirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study). Kardiologiia. 2020;60(6):15–29. [Russian: Мареев В.Ю., Орлова Я.А., Павликова Е.П., Мацкеплишвили С.Т., Краснова Т.Н., Малахов П.С. и др. Пульс-терапия стероидными гормонами больных с коронавирусной пневмонией (COVID-19), системным воспалением и риском венозных тромбозов и тромбоэмболий (исследование ПУТНИК). Кардиология. 2020;60(6):15-29]. DOI: 10.18087/cardio.2020.6.n1226
56. The RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL et al. Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report. New England Journal of Medicine. 2020; NEJMoa2021436. [Epub ahead of print]. DOI: 10.1056/NEJMoa2021436
57. Ramiro S, Mostard RLM, Magro-Checa C, van Dongen CMP, Dormans T, Buijs J et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. Annals of the Rheumatic Diseases. 2020;79(9):1143–51. DOI: 10.1136/annrheumdis-2020-218479
58. Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? JAMA Internal Medicine. 2020; [Epub ahead of print]. DOI: 10.1001/jamainternmed.2020.3313
59. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497–506. DOI: 10.1016/S0140-6736(20)30183-5
60. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62. DOI: 10.1016/S0140-6736(20)30566-3
61. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of Thrombosis and Haemostasis. 2020;18(6):1324–9. DOI: 10.1111/jth.14859
62. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of Thrombosis and Haemostasis. 2020;18(5):1094–9. DOI: 10.1111/jth.14817
63. Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Annals of Internal Medicine. 2020;173(4):268–77. DOI: 10.7326/M20-2003
64. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. Journal of the American College of Cardiology. 2020;76(1):122–4. DOI: 10.1016/j.jacc.2020.05.001
65. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research. 2020; 191:145–7. DOI: 10.1016/j.thromres.2020.04.013
66. Soylu K, Gedikli Ö, Ekşi A, Avcıoğlu Y, Soylu Aİ, Yüksel S et al. Neutrophil-to-lymphocyte ratio for the assessment of hospital mortality in patients with acute pulmonary embolism. Archives of Medical Science. 2016; 1:95–100. DOI: 10.5114/aoms.2016.57585
67. Price LC, McCabe C, Garfield B, Wort SJ. Thrombosis and COVID-19 pneumonia: the clot thickens! European Respiratory Journal. 2020;56(1):2001608. DOI: 10.1183/13993003.01608-2020
68. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thrombosis Research. 2020; 191:148–50. DOI: 10.1016/j.thromres.2020.04.041
69. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thrombosis Research. 2020;191:9–14. DOI: 10.1016/j.thromres.2020.04.024
70. Criel M, Falter M, Jaeken J, Van Kerrebroeck M, Lefere I, Meylaerts L и др. Venous thromboembolism in SARS-CoV-2 patients: only a problem in ventilated ICU patients, or is there more to it? European Respiratory Journal. 2020;56(1):2001201. DOI: 10.1183/13993003.01201-2020
71. Middeldorp S, Coppens M, Haaps TF, Foppen M, Vlaar AP, Müller MCA et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. Journal of Thrombosis and Haemostasis. 2020;18(8):1995–2002. DOI: 10.1111/jth.14888

72. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. New England Journal of Medicine. 2020;383(2):120–8. DOI: 10.1056/NEJMoa2015432
73. Bryce C, Grimes Z, Pujadas E, Ahuja S, Beasley MB, Albrecht R et al. Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. Pathology. 2020. Av. at: https://www.medrxiv.org/content/10.1101/2020.05.18.20099960v1.
74. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. The Lancet Rheumatology. 2020;2(7):e437–45. DOI: 10.1016/S2665-9913(20)30121-1
75. Dorward DA, Russell CD, Um IH, Elshani M, Armstrong SD, Penrice-Randal R et al. Tissue-specific tolerance in fatal Covid-19. Infectious Diseases (except HIV/AIDS). 2020. Av. at: https://www.medrxiv.org/content/10.1101/2020.07.02.20145003v1.
76. Iba T, Levi M, Levy JH. Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. Seminars in Thrombosis and Hemostasis. 2020;46(01):089–95. DOI: 10.1055/s-0039-1694995
77. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033–40. DOI: 10.1182/blood.2020006000
78. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. Journal of Thrombosis and Haemostasis. 2020;18(7):1738–42. DOI: 10.1111/jth.14850
79. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(4):844–7. DOI: 10.1111/jth.14768
80. Oudkerk M, Büller HR, Kuijpers D, van Es N, Oudkerk SF, McLoud TC et al. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. Radiology. 2020;201629. [Epub ahead of print]. DOI: 10.1148/radiol.2020201629
81. Llitjos J, Leclerc M, Chochois C, Monsallier J, Ramakers M, Auvray M et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of Thrombosis and Haemostasis. 2020;18(7):1743–6. DOI: 10.1111/jth.14869
82. Gavioli EM, Sikorska G, Man A, Rana J, Vider E. Current Perspectives of Anticoagulation in Patients with COVID-19. Journal of Cardiovascular Pharmacology. 2020;76(2):146–50. DOI: 10.1097/FJC.0000000000000861
83. Wise J. Covid-19 and thrombosis: what do we know about the risks and treatment? BMJ. 2020;369:m2058. DOI: 10.1136/bmj.m2058
84. Wang T, Chen R, Liu C, Liang W, Guan W, Tang R et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. The Lancet Haematology. 2020;7(5): e362–3. DOI: 10.1016/S2352-3026(20)30109-5
85. Spyropoulos AC, Ageno W, Barnathan ES. Hospital-based use of thromboprophylaxis in patients with COVID-19. The Lancet. 2020;395(10234):e75. DOI: 10.1016/S0140-6736(20)30926-0
86. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. Journal of the American College of Cardiology. 2020;75(23):2950–73. DOI: 10.1016/j.jacc.2020.04.031
87. Berghe TV, Linkermann A, Jouan-Lanhouet S, Walczak H, Vandenabeele P. Regulated necrosis: the expanding network of non-apoptotic cell death pathways. Nature Reviews Molecular Cell Biology. 2014;15(2):135–47. DOI: 10.1038/nrm3737
88. Jorgensen I, Miao EA. Pyroptotic cell death defends against intracellular pathogens. Immunological Reviews. 2015;265(1):130–42. DOI: 10.1111/imr.12287
89. Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. Nature Immunology. 2009;10(3):241–7. DOI: 10.1038/ni.1703
90. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The Role of Interleukin 6 During Viral Infections. Frontiers in Microbiology. 2019;10:1057. DOI: 10.3389/fmicb.2019.01057
91. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerging Microbes & Infections. 2020;9(1):1123–30. DOI: 10.1080/22221751.2020.1770129
92. Bulat V, Situm M, Azdajic MD, Likic R. Potential role of IL-17 blocking agents in the treatment of severe COVID-19? British Journal of Clinical Pharmacology. 2020; bcp.14437. [Epub ahead of print]. DOI: 10.1111/bcp.14437
93. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. The Lancet. 2020;395(10234):1407–9. DOI: 10.1016/S0140-6736(20)30858-8
94. Ucciferri C, Auricchio A, Di Nicola M, Potere N, Abbate A, Cipollone F et al. Canakinumab in a subgroup of patients with COVID-19. The Lancet Rheumatology. 2020;2(8):e457-ee458. DOI: 10.1016/S2665-9913(20)30167-3
95. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. New England Journal of Medicine. 2017;377(12):1119–31. DOI: 10.1056/NEJMoa1707914
96. Ministry of Health of Russian Federation. Temporary guidelines of the Ministry of health of the Russian Federation "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)". Version 4 of 27.03.2020. Moscow. Av. at: https://static-3.rosminzdrav.ru/system/attachments/attaches/000/049/877/original/COVID19_recomend_v4.pdf. 2020. [Russian: Министерство здравоохранения РФ. Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19)». Версия 4 (27.03.2020). Москва. Доступно на: https://static-3.rosminzdrav.ru/system/attachments/attaches/000/049/877/original/COVID19_recomend_v4.pdf]
97. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. Journal of Allergy and Clinical Immunology. 2020;146(1):137-146.e3. DOI: 10.1016/j.jaci.2020.05.019
98. Beringer A, Miossec P. Systemic effects of IL-17 in inflammatory arthritis. Nature Reviews Rheumatology. 2019;15(8):491–501. DOI: 10.1038/s41584-019-0243-5
99. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nature Reviews Drug Discovery. 2012;11(10):763–76. DOI: 10.1038/nrd3794
100. Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nature Reviews Immunology. 2020;20(5):271–2. DOI: 10.1038/s41577-020-0312-7
101. Carugno A, Gambini DM, Raponi F, Vezzoli P, Locatelli AGC, Di Mercurio M et al. COVID-19 and biologics for psoriasis: A high-epidemic area experience – Bergamo, Lombardy, Italy. Journal of the American Academy of Dermatology. 2020;83(1):292–4. DOI: 10.1016/j.jaad.2020.04.165
102. Di Lernia V, Bombonato C, Motolese A. COVID-19 in an elderly patient treated with secukinumab. Dermatologic Therapy. 2020;e13580. [Epub ahead of print]. DOI: 10.1111/dth.13580
103. Dagenais M, Skeldon A, Saleh M. The inflammasome: in memory of Dr. Jurg Tschopp. Cell Death & Differentiation. 2012;19(1):5–12. DOI: 10.1038/cdd.2011.159
104. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmunity Reviews. 2020;19(7):102567. DOI: 10.1016/j.autrev.2020.102567
105. Clancy CJ, Nguyen MH. Coronavirus Disease 2019, Superinfections, and Antimicrobial Development: What Can We Expect? Clinical Infectious Diseases. 2020; ciaa524. [Epub ahead of print]. DOI: 10.1093/cid/ciaa524

ISSN 0022-9040. Kardiologiia. 2020;60(9). DOI: 10.18087/cardio.2020.9.n1338

106. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care & Research. 2020;72(6):744–60. DOI: 10.1002/acr.24180
107. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. New England Journal of Medicine. 2019;381(26):2497–505. DOI: 10.1056/NEJMoa1912388
108. Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis. 2018; 269:262–71. DOI: 10.1016/j.atherosclerosis.2017.12.027
109. Lu Y, Chen J, Xiao M, Li W, Miller DD. An Overview of Tubulin Inhibitors That Interact with the Colchicine Binding Site. Pharmaceutical Research. 2012;29(11):2943–71. DOI: 10.1007/s11095-012-0828-z
110. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized with Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA Network Open. 2020;3(6): e2013136. DOI: 10.1001/jamanetworkopen.2020.13136
111. Montreal Heart Institute. Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19). ClinicalTrials.gov Identifier: NCT04322682. [Интернет] Available at: https://clinicaltrials.gov/ct2/show/NCT04322682
112. Population Health Research Institute. The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients. (COLCOVID). ClinicalTrials.gov Identifier: NCT04328480. [Интернет] Available at: https://clinicaltrials.gov/ct2/show/NCT04328480
113. Lomonosov Moscow State University Medical Research and Educational Center. COLchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial (COLORIT). ClinicalTrials.gov Identifier: NCT04403243. Av. at: https://clinicaltrials.gov/ct2/show/NCT04403243. 2020 r.
114. Carfì A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603–5. DOI: 10.1001/jama.2020.12603