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Proactive anti-inflammatory therapy in the advanced stages of a new coronavirus infection. Main results of the inpatient phase of the COLORIT study (Colchicin vs. Ruxolitinib and secukinumab in an open, prospective, randomized trial in patients with novel coronavirus infection COVID-19)

Aim	To evaluate clinical efficacy of the proactive anti-inflammatory therapy in patients hospitalized for COVID-19 with pneumonia and a risk of «cytokine storm».
Material and Methods	The COLORIT study was a comparative study with randomization into 4 groups: colchicine (n=21) 1 mg for the first 3 days followed by 0.5 mg/day through day 12 or discharge from the hospital; secukinumab 300 mg/day, s.c., as a single dose (n=20); ruxolitinib 5 mg, twice a day (n=10); and a control group with no anti-inflammatory therapy (n=22). The effect was evaluated after 12±2 days of inpatient treatment or upon discharge, what comes first. For ethical reasons, completely randomized recruitment to the control group was not possible. Thus, for data analysis, 17 patients who did not receive any anti-inflammatory therapy for various reasons not related with inclusion into the study were added to the control group of 5 randomized patients. Inclusion criteria: presence of coronavirus pneumonia (positive PCR test for SARS-CoV-2 RNA or specific clinical presentation of pneumonia; IDC-10 codes U07.1 and U07.2); C-reactive protein (CRP) concentration >60 mg/l or its threefold increase from baseline; at least 2 of 4 symptoms (fever >37.5 °C, persistent cough, shortness of breath with inspiratory rate >20 per min or blood saturation with oxygen <94% by the 7th – 9th day of disease. The study primary endpoint was changes in COVID Clinical Condition Scale (CCS-COVID) score. The secondary endpoints were the dynamics of CRP and changes in the area of lung lesion according to data of computed tomography (CT) of the lungs from the date of randomization to 12±2 days.
Results	All three drugs significantly reduced inflammation, improved the clinical course of the disease, and decreased the disease severity as evaluated by the CCS score: in the ruxolitinib group, by 5.5 (p=0.004); in the secukinumab group, by 4 (p=0.096); in the colchicine group, by 4 (p=0.017), and in the control group, by 2 (p=0.329). In all three groups, the CCS-COVID score was 2–3 by the end of observation period, which corresponded to a mild process, while in the control group, the score was 7 (p=0.005). Time-related changes in CRP were significant in all three anti-inflammatory treatment groups with no statistical difference between the groups. By the end of the study, changes in CT of the lungs were nonsignificant.
Conclusion	In severe COVID-19 with a risk of «cytokine storm», the proactive therapy with ruxolitinib, colchicine, and secukinumab significantly reduces the inflammation severity, prevents the disease progression, and results in clinical improvement.

Keywords	COVID-19; ruxolitinib; secukinumab; colchicine; “cytokine storm”; CCS-COVID
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The pandemic of the novel coronavirus disease (COVID-19) has been going on for 3 years. More than 600 million people have been infected and about 6.5 million patients have died worldwide, and more than 19 million and more than 380 thousand people, respectively, in the Russian Federation. During the first waves of the pandemic in 2020 when the Alpha variant of SARS-CoV-2 dominated and before the introduction of vaccination, the mortality rate was lower in the Russian Federation than in the world – 1.9% versus 2.3%. In 2021, with the predominance of the Delta variant and low herd immunity, it increased to 3.4% in the Russian Federation, and decreased to 1.8% in the world during mass vaccination. In 2022, against the background of the widespread highly contagious, but less dangerous variant Omicron and its subvariants, mortality decreased to 0.85% in the Russian Federation and 0.32% worldwide. However, the prognosis of patients with COVID stays unfavourable [1, 2]. Therefore, the problem of specific effective treatment of COVID-19 remains in the spotlight.

If it is not possible to prevent the development of the disease or cope with viremia, a patient with COVID-19 can quickly develop autoimmune and bacterial inflammatory complications, even a cytokine storm, thrombotic complications and multiple organ failure. In these cases, it is necessary to consider conducting preemptive anti-inflammatory therapy to prevent potentially fatal complications.

The onset or persistence of fever, asthenia, lymphopenia and elevated levels of C-reactive protein (CRP) by day 7–9 day of the Alpha variant and already by day 3–4 of the Delta variant of SARS-CoV-2 signal the need for such treatment [3]. Although the administration of glucocorticoids (GCs), mainly oral dexamethasone 6–8 mg/day, is the most well-proven method of treatment [4, 5], it is of great interest to find other options for preemptive anti-inflammatory therapy. In addition to GCs, different classes of drugs were administered for preemptive anti-inflammatory therapy, including drugs listed in the "Temporary guideline of the Ministry of Health of the Russian Federation for the management of COVID-19": Janus kinase (JAK) inhibitors 1/2, interleukin (IL) – 17A inhibitors, IL-6 receptor antagonists or IL-6 blocker, IL-1B blockers and some other recombinant drugs, the efficacy of which has not yet been unequivocally proven, and they remain experimental agents [6].

Randomized clinical trial (RCT) "COLchicine cOmpared to Ruxolitinib and secukinumab in an open-label prospecTive randomized trial in patients with COVID-19 (COLORIT)" was carried out at the Lomonosov Moscow State University [7].

Material and Methods

The COLORIT trial was designed as a comparative open-label randomized study. Patients were randomized to four groups (2:2:1:2): colchicine 1 mg on day 1–3 after the beginning of anti-inflammatory therapy followed 0.5 mg/day until day 12±2 or discharge, whatever was earlier; a single dose of IL-17 inhibitor secukinumab 300 mg/day subcutaneously once; selective JAK-1 and JAK-2 inhibitor ruxolitinib 5 mg bid, and the control group without preemptive anti-inflammatory therapy. Randomization was performed by the sealed code envelope method. Enrollment in the three active groups was purely randomized according to the trial design (2:2:1), but only 5 patients were randomized to the control group because most hospitalized patients had severe disease requiring active treatment. Seventeen patients who did not receive anti-inflammatory therapy were additionally included in the control group. The effect was assessed after 12 ± 2 days of hospital treatment or before discharge, whatever was earlier, and if possible, 45 days after discharge.

Inclusion criteria

1. Documented COVID-19-associated pneumonia (positive PCR for SARS-CoV-2 RNA and/or apparent specific presentation of pneumonia: ICD-10 U07.1 and U07.2). Signs of lung lesion were evaluated per the clinical guideline (Order of the Moscow Department of Health No. 355 dated 06.04.2020 "On the algorithm of action at the admission of patients with suspected community-acquired pneumonia of presumed coronavirus origin" [8]; CT diagnosis of COVID-19: organization, methodology, interpretation of the results – 2020 – I [9]). Patients were randomized on day 2 [1; 4] day after admission to the hospital, which corresponded to day 6–11 of the disease.
2. CRP > 60 mg/L or its 3-fold increase by day 8–14 of the disease.
3. At least two of the four signs: fever > 37.5°C; persistent cough; dyspnea with respiratory rate (RR) > 20 brpm, or reduced oxygen saturation < 94% in atmospheric air.

Exclusion criteria

Exclusion criteria were common for such trials and are published on the website [7].

Changes in the SHOCS-COVID score were the primary endpoint. The score included the assessment of clinical state (hyperthermia, dyspnea, oxygen saturation, the need for mechanical ventilation), the degree of inflammation (CRP levels), markers of clotting (D-dimer), the degree of lung lesion according to computed tomography (CT) and the duration of hospital treatment [3, 10].

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The secondary endpoints included the evolution of inflammation (CRP levels), coagulopathy (D-dimer), and area of lung lesion according to CT findings.

Total blood count, biochemical blood test, and lung CT imaging were performed in all patients on day 1–2 of hospital treatment, before randomization. Data obtained on the day of randomization or over the previous 2 days were used as the baseline for repeated CT examinations. CT examination was repeated in 12±2 days or at discharge, whatever was earlier. If possible, the examination was repeated on day 45 of treatment, but this article discusses the in-hospital outcomes. In addition to the Symptomatic Hospital and Outpatient Clinical score for COVID-19 (SHOCS-COVID) [10], we used the NEWS-2 distress syndrome severity score [11] to objectify the severity of the patient's clinical condition and adequately assess the effects of the therapy.

The study included 73 patients: 10 patients in the group of ruxolitinib 5 mg bid for 12 days or until discharge, 20 patients received a single injection of secukinumab 300 mg subcutaneously with the control examination in 12 days or before discharge, 21 patients were treated

Table 1. Baseline characteristics of patients of the COLORIT trial

Parameter	Ruxolitinib (n = 10)	Secukinumab (n = 20)	Colchicine (n = 21)	Control (n = 22)	P (comparison of four groups)
General characteristics					
Age, years	59.5 [58.2; 67.8]	56.0 [50.8; 63.2]	62.0 [55.0; 70.0]	64.5 [45.2; 77.8]	0.685
BMI, kg/m^2	28.0 [24.9; 30.7]	31.0 [28.6; 37.1]	30.9 [27.1; 32.9]	29.6 [27.0; 32.4]	0.173
Male, n (%)	8 (80.0)	9 (45.0)	14 (66.7)	16 (72.7)	0.179
AH, n (%)	5 (50.0)	15 (75.0)	14 (66.7)	13 (59.1)	0.556
CAD, n (%)	2 (20.0)	3 (15.0)	3 (14.3)	4 (18.2)	1.000
DM, n (%)	0	9 (45.0)	3 (14.3)	2 (9.09)	0.005
Clinical parameters					
Body temperature, °C	36.6 [36.3; 36.9]	37.0 [36.7; 37.7]	37.4 [36.9; 37.8]	36.9 [36.6; 37.6]	0.046
RR, breaths per min	18.0 [17.0; 18.0]	18.5 [17.8; 20.0]	18.0 [17.0; 20.0]	19.0 [18.0; 21.8]	0.311
HR, bpm	79.0 [69.5; 81.5]	79.0 [67.0; 83.5]	76.0 [72.0; 82.0]	81.0 [74.2; 87.8]	0.500
SBP, mm Hg	120 [114; 132]	120 [110; 122]	120 [112; 120]	125 [115; 129]	0.657
SaO_2, %	92.0 [89.0; 93.0]	95.0 [88.0; 96.2]	93.0 [92.0; 96.0]	94.5 [93.0; 96.0]	0.384
SaO_2 < 94 %, n (%)	7 (77.8)	8 (40.0)	10 (52.6)	6 (30.0)	0.108
Oxygen support, n (%)	8 (80.0)	10 (52.6)	14 (66.7)	12 (54.5)	0.456
Mechanical ventilation at baseline, n (%)	0	1 (5.26)	0	1 (4.55)	0.815
Biochemical variables					
CRP, mg/dL	122 [94.0; 181]	135 [70.2; 190]	99.4 [57.7; 116]	91.5 [59.2; 131]	0.193
D-dimer, μg/dL	0.83 [0.51; 1.33]	0.56 [0.46; 1.31]	0.87 [0.58; 1.24]	1.12 [0.79; 1.37]	0.296
Fibrinogen, g/L	6.60 [5.99; 7.62]	6.83 [5.64; 7.45]	6.14 [4.97; 6.72]	6.32 [5.66; 7.28]	0.512
Lymphocytes, × 10^9/L	1.22 [1.00; 1.62]	0.98 [0.83; 1.65]	0.99 [0.83; 1.34]	1.06 [0.79; 1.55]	0.876
Neutrophils, × 10^9/L	4.61 [2.89; 5.74]	4.28 [2.90; 7.09]	2.99 [2.56; 4.62]	4.47 [3.07; 5.64]	0.226
NLR	2.84 [2.16; 6.30]	4.41 [2.20; 8.33]	2.93 [2.39; 3.65]	3.53 [2.03; 6.24]	0.709
Platelets, × 10^9/L	251 [190; 316]	188 [152; 226]	230 [150; 247]	184 [161; 269]	0.285
LCR	10.8 [6.14; 15.3]	7.55 [4.95; 15.3]	14.0 [8.01; 22.5]	12.5 [7.88; 21.9]	0.331
Glucose, mmol/L	6.10 [5.66; 6.70]	6.07 [5.34; 7.28]	5.64 [5.12; 6.27]	6.19 [5.79; 6.55]	0.295
Creatinine, mmol/L	95.5 [80.2; 112]	94.0 [74.5; 111]	84.0 [76.0; 101]	88.5 [65.2; 104]	0.613
GFR, mL/min/1.73 m^2 (CKDEpi)	69.0 [60.2; 82.8]	70.0 [50.5; 92.0]	77.0 [60.0; 84.0]	83.0 [66.0; 93.2]	0.526
Total evaluation of the severity					
Pulmonary CT (% of the lesion)	28.9 [14.8; 39.1]	24.2 [11.1; 55.2]	17.5 [9.40; 31.7]	25.6 [12.6; 35.8]	0.619
SHOCS-COVID, score	9.00 [7.00; 10.0]	6.00 [6.00; 10.0]	8.00 [6.00; 8.50]	7.00 [6.00; 10.0]	0.902
NEWS-2, score	5.00 [4.00; 8.00]	3.00 [1.00; 7.00]	5.00 [3.00; 7.00]	5.00 [3.75; 7.00]	0.769
Concomitant treatment					
GCs, n (%)	–	–	–	–	0.078
GCs, oral, n (%)	3 (30.0)	5 (26.3)	2 (9.52)	0	–
GCs, inhalational, n (%)	0	1 (5.26)	1 (4.76)	0	–

BMI, body mass index; AH, arterial hypertension; CAD, coronary artery disease; DM, diabetes mellitus; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; SaO_2, oxygen saturation; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; GFR, glomerular filtration rate; CT, computed tomography; GC, glucocorticoid. SHOCS-COVID, Symptomatic Hospital and Outpatient Clinical Score for COVID-19

with colchicine 1 mg on day 1 followed by 0.5 mg/day for 12 days or until discharge, and 22 patients formed the control group. The data are presented in Table 1.

All four groups of patients were balanced by the majority of indicators, some insignificant differences can be explained by a low number of observations. All patient groups showed markedly elevated levels of CRP and D-dimer and a decreased lymphocyte/CRP ratio.

The total NEWS-2 score was 5 in three groups, except for the secukinumab group, i.e. it was close to the threshold when it is recommended to consider transferring patients to the intensive care unit. There were no such patients in this study.

The median SHOCS score was 9, 6, 8, and 7 in the ruxolitinib, secukinumab, colchicine, and control groups, respectively. Patients received antibiotic and anticoagulant therapy in all groups following the treatment protocol approved by the Lomonosov Moscow State University [12].

A total of 10 patients in the three active treatment groups received low-dose oral GCs (ruxolitinib 30%, secukinumab 26%, and colchicine 10%) and two patients (with concomitant chronic obstructive pulmonary disease (COPD)) received inhalations. GCs were not administered in the control group. As a result, 12 (23.5%) patients receiving preemptive anti-inflammatory therapy administered GCs, which corresponded to the guideline of the Ministry of Health of the Russian Federation then in force.

Statistical analysis

The quantitative data are described as the median and the interquartile range (Me [25th percentile; 75th percentile]). The quantitative variables were compared between groups using the Kruskal-Wallis method. In the case of a statistically significant difference, a pairwise comparison using the Mann-Whitney test was performed to compare the four groups. The qualitative data is presented as the absolute and relative values. The significance of intergroup differences in qualitative characteristics was assessed using the chi-square test and two-tailed Fisher's exact test. The intragroup changes were compared using the Wilcoxon signed-rank test for quantitative variables and the McNemar's test for qualitative data. The critical significance threshold for the statistical hypotheses was set as $p = 0.05$.

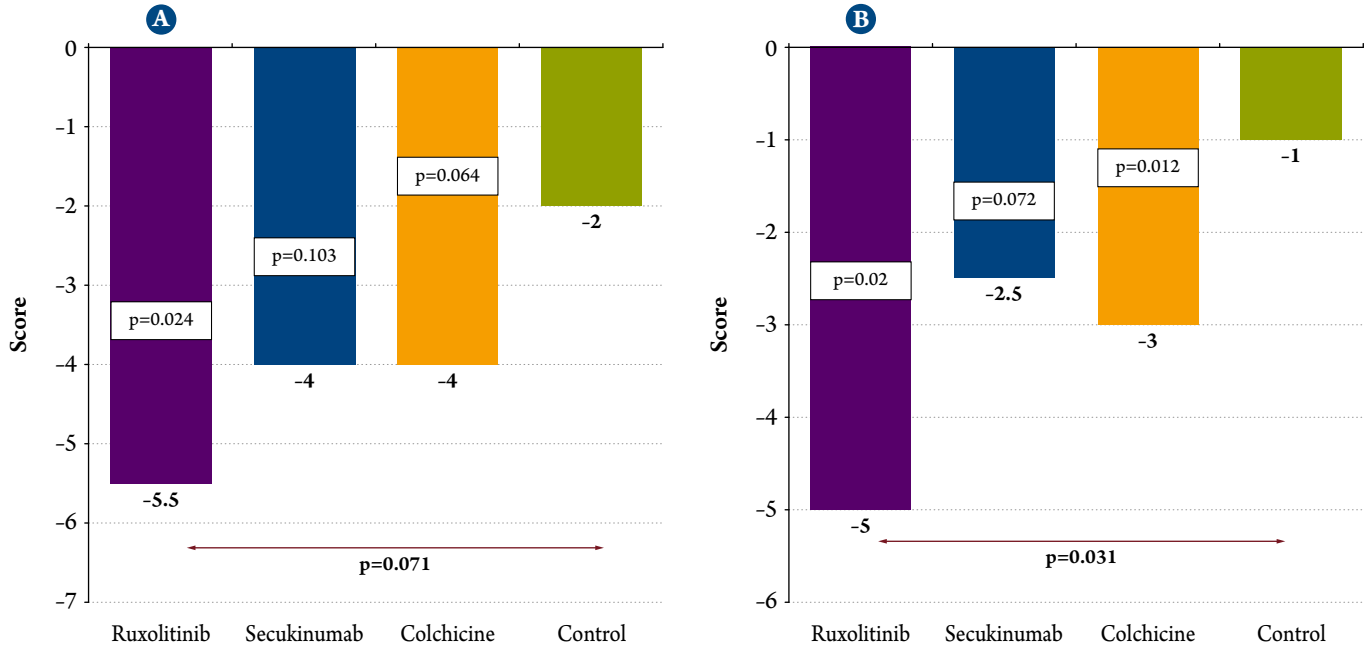
The trial protocol was approved by the local ethics committee of the Lomonosov Moscow State University. Patients signed the voluntary informed consent to participate in the study.

Results

Evolution of the disease severity was assessed using the integral SHOCS-COVID score in all groups on day 12st±2 of treatment or before discharge, whatever was earlier (Figure 1).

There was a statistically significant decrease in the SHOCS-COVID score in all three active treatment groups. The maximum and statistically significant

Figure 1. Changes in the SHOCS-COVID score (integral assessment of the total severity of disease manifestations (**A**)) and the NEWS-2 score (clinical assessment of the severity of distress syndrome (**B**)) during treatment with ruxolitinib (n=10), secukinumab (n=20), colchicine (n=21), and without anti-inflammatory therapy (n=22) on day 12±2 of treatment or before discharge



p at the bottom of the figure – comparison of 4 groups; p inside the columns – comparison of each anti-inflammatory therapy group with the control group.

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differences from the control group were observed in the ruxolitinib group. The scores decreased minimally in the control group, but in general, the differences were statistically significant in either of the four groups (p=0.071). This may be due to the low numbers of patients and some differences in the effects of the three different anti-inflammatory drugs.

The pooled anti-inflammatory therapy group (n=51) and the control group (n = 22) were compared to clarify the situation. In this case, the SHOCS-COVID scores decreased by 3.97 ± 4.01 in the treatment group and only by 0.94 ± 4.63 in the control group, with the differences being statistically significant (p = 0.026).

In addition, the final (post-treatment) values of other indicators are presented in Table 2.

The post-treatment SHOCS-COVID score was 2–3 in all three groups at the end of the observation, which corresponds to a mild process, and this indicator remained 7 in the control group (p=0.005), i.e., the condition remained moderately severe in patients who did not receive preemptive anti-inflammatory therapy.

Figure 1, B shows the evolution of clinical symptoms characterizing the severity of respiratory distress syndrome. Among the three groups of anti-inflammatory therapy, a statistically significant decrease in the NEWS-2 score was achieved in the ruxolitinib and colchicine groups, and there was only a trend to a decrease in the secukinumab group (p=0.072). However, the differences with the control group were statistically significant (p=0.031). By the end of treatment (Table 2), the NEWS-2 scores were 0–1 in the anti-inflammatory therapy groups, which indicates the successful management of distress syndrome. In the control group, this indicator corresponded to moderate severity of symptoms requiring hospital treatment in a therapeutic department.

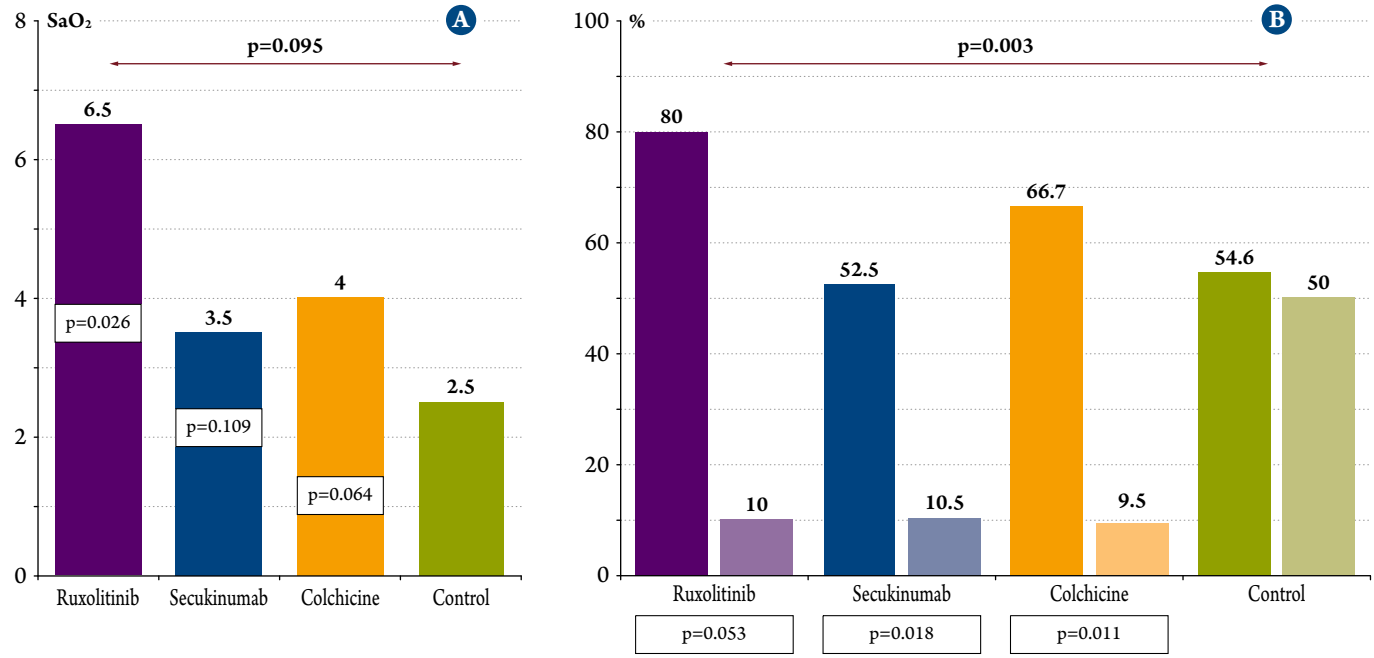
Figure 2, A shows changes in SaO_2. At baseline, 77.8% of patients receiving ruxolitinib had SaO_2 less than

Table 2. Final data of patients in the COLORIT trial on day 12 ± 2 of hospital treatment or before discharge, whatever was earlier

Parameter	Ruxolitinib (n = 10)	Secukinumab (n = 20)	Colchicine (n = 21)	Control (n = 22)	P (comparison of four groups)
Clinical parameters					
Body temperature, °C	36.6 [36.5; 36.7]	36.5 [36.3; 36.5]	36.5 [36.2; 36.5]	36.5 [36.3; 36.8]	0.416
RR, breaths per min	17.0 [16.0; 18.0]	17.0 [16.0; 18.0]	16.0 [16.0; 17.2]	18.0 [17.0; 19.0]	0.009
HR, bpm	76.0 [69.2; 76.0]	76.0 [69.0; 80.2]	74.0 [68.0; 76.0]	80.0 [73.0; 85.8]	0.091
SBP, mm Hg	120 [118; 124]	120 [114; 125]	120 [120; 122]	119 [111; 124]	0.808
SaO_2, %	97.0 [97.0; 98.0]	98.0 [97.0; 99.0]	98.0 [97.0; 99.0]	96.5 [92.0; 98.0]	0.042
SaO_2 < 94 %, n (%)	0	1 (5.56)	1 (5.00)	6 (30.0)	0.028
Oxygen support, n (%)	1 (10.0)	2 (10.5)	2 (9.52)	11 (50.0)	0.003
Mechanical ventilation, final, n (%)	1 (10.0)	0	1 (4.76)	2 (9.09)	0.670
Biochemical variables					
CRP, mg/dL	6.58 [5.37; 28.6]	9.98 [4.46; 17.8]	4.23 [2.47; 11.1]	22.8 [7.62; 95.9]	0.012
D-dimer, μg/dL	0.95 [0.46; 1.40]	0.77 [0.42; 1.22]	0.66 [0.36; 1.21]	1.14 [0.65; 2.07]	0.450
Fibrinogen, g/L	5.37 [5.06; 6.57]	5.24 [4.38; 5.81]	4.16 [3.83; 5.34]	6.40 [5.79; 6.75]	0.018
Lymphocytes, × 10^9/L	1.96 [1.67; 2.49]	1.86 [1.42; 2.30]	1.83 [1.50; 2.22]	1.38 [1.03; 1.89]	0.193
Neutrophils, × 10^9/L	3.44 [2.85; 4.00]	3.65 [2.91; 4.72]	2.89 [2.50; 4.21]	3.79 [2.74; 6.17]	0.488
NLR	1.92 [1.17; 2.31]	1.88 [1.53; 2.65]	1.72 [1.27; 1.87]	2.79 [1.63; 3.14]	0.111
Platelets, × 10^9/L	416 [327; 545]	318 [272; 387]	361 [299; 374]	352 [314; 428]	0.174
LCR	285 [89.8; 470]	199 [93.8; 423]	427 [155; 731]	60.9 [11.2; 216]	0.016
Glucose, mmol/L	5.02 [4.90; 5.82]	5.97 [5.11; 8.14]	5.66 [5.24; 6.55]	5.09 [4.67; 5.63]	0.090
Creatinine, mmol/L	95.5 [75.8; 105]	77.0 [69.0; 90.0]	88.0 [76.0; 94.0]	83.5 [74.2; 96.0]	0.386
GFR, mL/min/1.73 m^2 (CKDEpi)	72.0 [65.2; 87.5]	78.0 [72.5; 94.0]	77.0 [74.0; 86.0]	85.5 [68.0; 97.2]	0.625
Total evaluation of the severity					
CT (% of the lesion)	19.2 [10.2; 26.8]	23.9 [8.60; 51.9]	13.4 [6.95; 34.2]	34.0 [15.5; 49.1]	0.232
SHOCS-COVID, score	3.00 [2.00; 4.00]	3.00 [2.00; 4.00]	2.00 [2.00; 3.25]	7.00 [4.00; 9.00]	0.005
NEWS-2, score	1.00 [0.00; 3.00]	0.00 [0.00; 1.00]	1.00 [0.00; 3.00]	3.00 [2.75; 5.25]	0.002
Time in hospital, days	12.0 [10.2; 14.0]	11.0 [9.75; 13.0]	13.0 [11.0; 15.0]	17.5 [12.5; 19.8]	0.026
Death + VTEs, n (%)	0	0	1 (4.76)	2 (9.09)	0.637

RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; SaO_2, oxygen saturation; CRP = C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; BMI, body mass index; GFR, glomerular filtration rate; CT, computed tomography; VTE, venous thromboembolic event.

Figure 2. Changes in SaO_2 CRP (**A**) and the need for oxygen support (**B**) during the administration of ruxolitinib (n=10), secukinumab (n=20), colchicine (n=21), and without anti-inflammatory therapy (n=22) by day 12±2 of treatment or discharge, whatever was earlier



A – oxygen saturation delta; **B** – the need for oxygen support.

94%, the median SaO_2 increased by 6.5% (p=0.026) to 97% during treatment, and SaO_2 higher than 94% was registered in all patients (see Table 2). In the secukinumab and colchicine groups, 40% and 52.6% of patients had baseline SaO_2 less than 94%, which increased by 3.5% and 4.0%, respectively, and reached 98% in both groups. In the control group, mean SaO_2 remained lower than in the active treatment groups – 96.5% (p=0.042), and less than 94% in the same 30% of patients as at baseline (Table 2).

Figure 2, B shows the dynamic of the need for oxygen support. The need for auxiliary ventilation decreased to 10% in all three groups of anti-inflammatory therapy, and it did not change in the control group. Differences were statistically significant between all four groups (p=0.003).

Changes in the markers of inflammation severity are shown in Figure 3. Baseline CRP (the main secondary endpoint) was 18–27 times higher than normal in all patient groups. CRP levels normalized in the colchicine group (<5.0 mg/dL) and remained twice the upper limit of normal in the ruxolitinib and secukinumab groups (< 10.0 mg/dL). According to the standards of the Lomonosov Moscow State University, CRP levels ≤ 10 mg/dL were considered sufficient for deinstitutionalization. This indicator remained increased in the control group by more than 4 times – 22.8 [7.62; 95.9] mg/dL. Differences were statistically significant in all four groups (p = 0.012).

Figure 3, B shows the evolution of one of the most accurate markers of the severity of systemic inflammation, namely the lymphocyte/CRP ratio, the normal value of which should be > 100 units [13].

This indicator was 7–13 times lower than normal in all four groups. As can be seen, this indicator increased considerably and statistically significant in all three groups of anti-inflammatory therapy. The increase was 3.5, 5, and 7.3 times less in the control group than in the secukinumab, ruxolitinib, and colchicine groups, respectively. Differences were statistically significant in all four groups (p = 0.013).

Another secondary endpoint was the analysis of the risk of coagulopathy and the risk of thrombotic and thromboembolic complications by the levels of D-dimer. This indicator was moderately elevated in all groups at baseline and did not normalize in either with no differences between the groups. Hyperfibrinogenemia (fibrinogen level of 6.60 g/l in the ruxolitinib group, 6.83 g/l in the secukinumab group, 6.14 g/l in the colchicine group and 6.32 in the control group at a rate of 2–4 g/l), as a manifestation of systemic inflammation, is characteristic of COVID-associated coagulopathy. There was a clear post-treatment trend of a decrease in fibrinogen levels in all three groups of preemptive anti-inflammatory therapy, unlike the control group (p=0.018).

When assessing the degree of lung involvement in the pathological process, it should be kept in mind that

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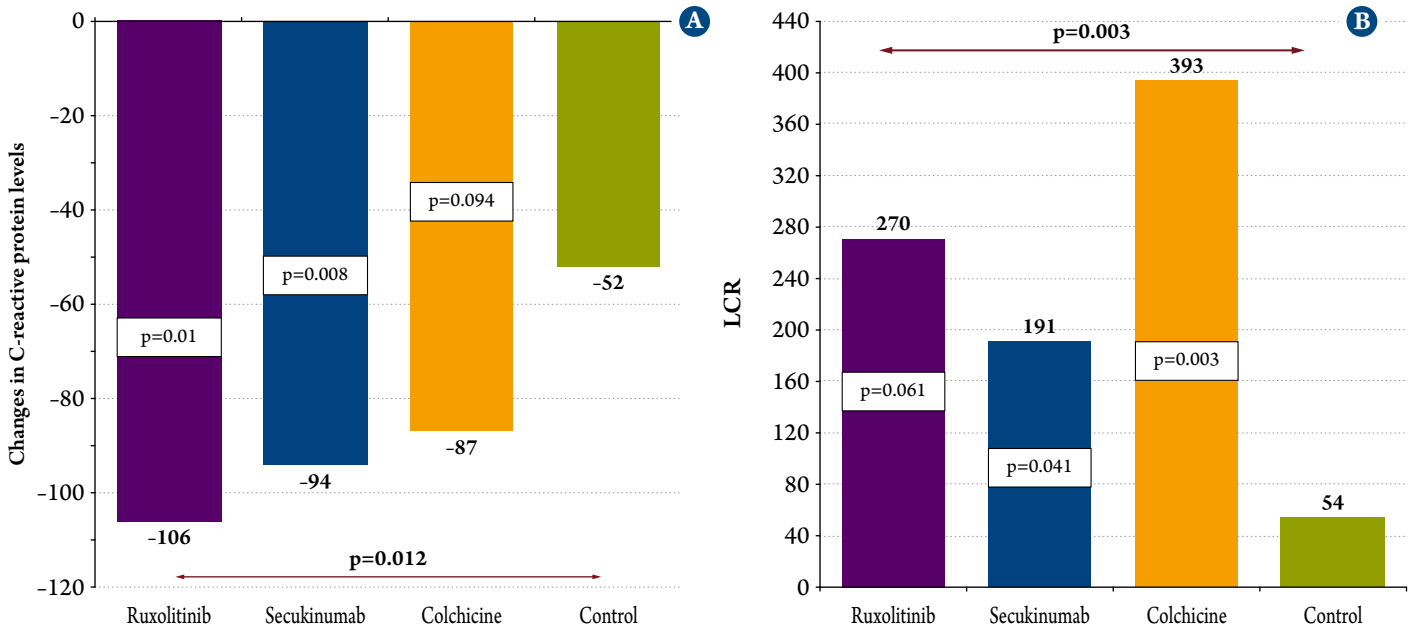
Figure 3. Changes in the levels of CRP (**A**) and LCR (**B**) during the administration of ruxolitinib (n=10), secukinumab (n=20), colchicine (n=21), and without anti-inflammatory therapy (n=22) by day 12±2 of treatment or discharge, whatever was earlier



CRP, C-reactive protein; LCR, lymphocyte-to-C-reactive protein ratio.

the morphological picture improvement is delayed compared to the clinical and biochemical indicators. As seen in Figure 4, A, the area of lung lesion increased in the control group (by 8.96%), and it tended to decrease in the groups of anti-inflammatory treatment (by a total of 0.75%, differences with the control group p = 0.08).

Figure 4, B shows the duration of hospital treatment. The duration of hospital stay was the shortest in the secukinumab group. Patients of the control group required considerably longer hospital treatment – 17.5 days (p=0.026).

Table 3 shows the comparative evolution of clinical and biochemical indicators and the severity of COVID-19 in three groups of anti-inflammatory therapy.

According to the data presented, there were no statistically significant differences in the effects of drugs and changes in the primary endpoint (SHOCS-COVID scores) and secondary endpoints (changes in CRP, D-dimer, and area of lung lesion according to CT).

Discussion

The COLORIT trial studied the treatment of patients with moderate to severe COVID-19 and the risk of a cytokine storm. Thus, the question arises about additional anti-inflammatory therapy. The following can be the signals to it: the onset or preservation of fever above 37.5 °C, asthenia (severe weakness, apathy, cognitive decline, brain fog), lymphopenia (< 1200/μL), and elevated CRP by day 7–9 of the disease in the case of Alpha and Beta variants and day 3–4 in the Delta variant of SARS-CoV-2 [14, 15].

The COLORIT protocol included the administration of drugs with different mechanisms of anti-inflammatory action: JAK-1 and JAK-2 inhibitor ruxolitinib that activates the transmission of impulses through the transporter system (STAT) and modulates the autoimmune response [16]; interleukin-17 (IL-17) inhibitor secukinumab that interrupts the stimulation of endothelial and epithelial cells and reduces the release of cytokines and the breakdown of compensatory autoimmune reactions [17]; well-known anti-inflammatory drug colchicine used to relieve gout attacks [18]. The main anti-inflammatory effect of this drug in COVID-19 is associated with inflammasome blockade and an indirect decrease in cytokine overproduction [19]. Moreover, colchicine is able to slow down the penetration of the SARS-CoV-2 viruses into the cell nucleus and inhibit replication, reducing the viral load by tubulin blockade [20].

The first analysis of the COLORIT trial (case-control) demonstrated a clinically significant positive anti-inflammatory effect of colchicine (normalization of CRP levels, statistically significant increase in LCR, and normalization of the SHOCS-COVID scores) compared to the control group [21]. However, the debate continues about the efficacy of colchicine. There have been many controlled trials of colchicine worldwide. The latest meta-analysis included 8 controlled trials (including

Figure 4. Changes in the lung lesion area (A) and duration of hospital treatment (B) during the administration of ruxolitinib (n=10), secukinumab (n=20), colchicine (n=21), and without anti-inflammatory therapy (n=22) after 12±2 days of treatment

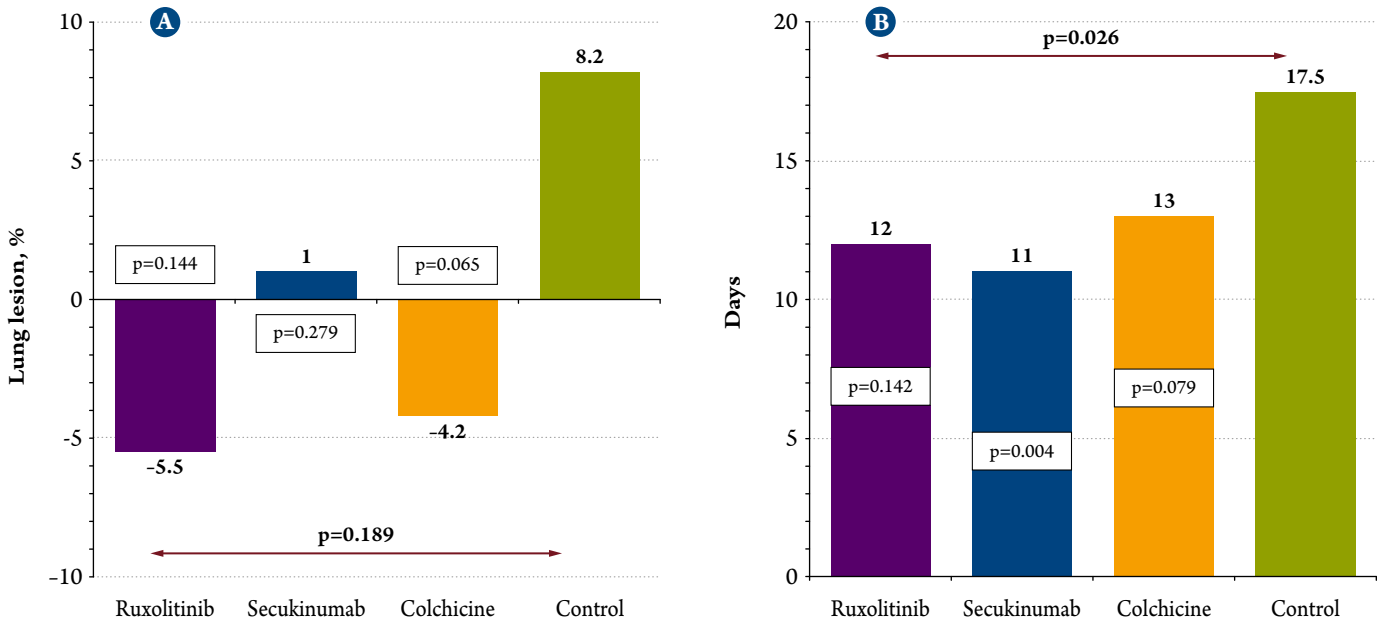


Table 3. Evolution of COVID-19 patients receiving anti-inflammatory treatment with ruxolitinib (n=10), secukinumab (n=20), or colchicine (n=21)

Parameter	Ruxolitinib (n = 10)	Secukinumab (n = 20)	Colchicine (n = 21)	P (comparison of three groups)
Clinical characteristics				
Body temperature, median, °C	–0.10 [–0.55; 0.30]	–0.60 [–1.20; 0.00]	–0.90 [–1.20; –0.40]	0.025
RR, median, bpm	0.00 [–2.00; 0.00]	–1.00 [–3.00; 0.00]	–2.00 [–4.00; –1.00]	0.286
HR, median, bpm	–3.50 [–12.75; 4.75]	–4.50 [–10.50; 4.25]	–3.00 [–12.00; 3.00]	0.966
SBP, median, mm Hg	–4.00 [–10.00; 6.00]	0.00 [–4.25; 5.00]	0.00 [–8.00; 10.0]	0.733
SaO_2, median, %	6.50 [4.00; 9.50]	3.50 [1.25; 6.00]	4.00 [1.00; 6.00]	0.633
Biochemical variables				
CRP, median, mg/dL	–105.76 [–164.9; –78.5]	–94.46 [–156.2; 65.8]	–86.69 [–110.1; –41.1]	0.332
D-dimer, median, μg/dL	–0.23 [–0.58; 0.06]	–0.05 [–0.49; 0.31]	–0.23 [–0.88; 0.19]	0.679
Lymphocytes, median, × 10^9/L	0.63 [0.42; 0.93]	0.56 [0.23; 1.05]	0.72 [0.53; 0.97]	0.529
Neutrophils, median, × 10^9/L	–1.08 [–2.19; 0.36]	–0.08 [–0.64; 0.38]	0.08 [–0.75; 1.07]	0.525
Creatinine, median, mmol/L	–4.50 [–7.00; 3.75]	–5.50 [–23.75; 1.50]	–3.00 [–11.00; 8.00]	0.583
GFR [CKDEpi], median, mL/min/1.73 m^2	4.50 [–2.00; 7.75]	5.00 [–3.00; 20.8]	4.00 [–5.00; 8.00]	0.538
Glucose, median, mmol/L	–0.64 [–0.79; –0.23]	–0.52 [–0.81; 2.68]	–0.03 [–0.26; 0.69]	0.332
Fibrinogen, median, g/L	–1.42 [–2.22; 0.35]	–1.21 [–2.18; –0.84]	–1.22 [–2.27; 0.26]	0.959
Platelets, median, × 10^9/L	194 [116; 251]	133 [54.5; 196]	127 [69.0; 175]	0.234
NLR, median	–0.95 [–2.42; –0.65]	–1.12 [–3.63; –0.22]	–1.44 [–2.01; –0.67]	0.950
LCR, median	270 [82.8; 462]	191 [88.2; 413]	393 [147; 727]	0.341
Total evaluation of the severity				
Lung CT (%), median	–5.50 [–9.07; 2.65]	1.00 [–6.55; 10.5]	–4.20 [–9.88; 2.22]	0.484
SHOCS-COVID score, median	–5.50 [–6.00; –5.00]	–4.00 [–6.00; –2.00]	–4.00 [–6.00; –2.25]	0.539
NEWS-2 score, median	–5.00 [–5.25; –3.00]	–2.50 [–4.50; –0.25]	–3.00 [–5.00; –2.00]	0.545

RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; SaO_2, oxygen saturation; CRP, C-reactive protein; BMI, body mass index; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; CT, computed tomography; SHOCS-COVID, Symptomatic Hospital and Outpatient Clinical Score for COVID- 19.

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COLORIT) and more than 16 thousand patients. In the largest of these trials, RECOVERY, colchicine did not affect the prognosis in hospitalized patients with COVID-19 [22]. The other seven (relatively small) trials demonstrated a potent anti-inflammatory effect of colchicine and a significant improvement in prognosis [23]. The RECOVERY trial included all hospitalized patients with COVID-19 and the mean CRP of 86 mg/dL, which is much lower than in the COLORIT program. A recent randomized comparative ACT Inpatient Trial (more than 2,600 patients) has demonstrated an anti-inflammatory effect but no effect on the prognosis [24]. All patients hospitalized with COVID-19 were included and the CRP level was 3 times less than in the COLORIT program. It should be noted that patients included in the first 13 weeks had a significantly higher risk of death and mechanical ventilation, and there was a trend to a decrease in the risk of death. Later, when less dangerous variants appeared, mortality decreased, and colchicine had no effect [25].

In our study, the effects of colchicine were compared with JAK inhibitor ruxolitinib and IL-17 inhibitor secukinumab. There were no statistically significant differences in the baseline severity of the patient's condition, although the SHOCS score was 9 in the ruxolitinib group and 6 in the secukinumab group. All three drugs statistically significantly reduced the degree of inflammation, improved the clinical course of the disease, and reduced the severity of the SHOCS-COVID score and the duration of hospital treatment. As seen in Table 3, there were no statistically significant differences in the effects of the three drugs of interest, but the highest cumulative effect was detected in the ruxolitinib group and slightly less effect in the secukinumab group.

There is no absolute certainty in the use of any anti-inflammatory drug in the treatment of severe forms of COVID-19 except for GCs. However, there are some hopes. A Cochrane meta-analysis of 6 trials (and 4 trials with baricitinib) on the use of JAK inhibitors showed a statistically significant reduction in mortality by 28% by day 28 (n = 11,145) and by 31% by day 60 (2 trials, n=1,626). A minimal impact on the clinical condition and the need for oxygen support was revealed. However, trials conducted in the Russian Federation showed the positive effect of baricitinib on inflammation and the degree of lung lesions [26]. A controlled trial with ruxolitinib fully confirmed our findings on the reduction of lung lesions according to CT, although the decrease in mortality was statistically insignificant [27]. Thus, JAK inhibitors, including ruxolitinib, are a real option for preemptive anti-inflammatory therapy.

The third drug of interest was IL-17 inhibitor secukinumab indicated mainly for psoriasis [28]. It was slightly inferior to ruxolitinib and colchicine in the degree of anti-inflammatory effect and effect on the clinical condition of patients with COVID-19. However, the positive effect of secukinumab was not confirmed in either trial. In the BISHOP study, for example, it was safe but did not affect the prognosis of patients, however, the baseline level of CRP was 43 mg/dL in that study, which casts doubt on the indications for preemptive anti-inflammatory therapy [29]. There is more experience in the Russian Federation in using another IL-17 blocker netakimab in the treatment of COVID-19. One of the earliest trials demonstrated an anti-inflammatory effect and better oxygenation without a statistically significant decrease in the need for respiratory support and risk of death [30]. A retrospective study with the inclusion criteria assuming baseline CRP levels >60 mg/dL, as in the COLORIT program, demonstrated excellent results, and netakimab was superior to IL-6 inhibitor tocilizumab in the anti-inflammatory and clinical efficacy [15]. Similarly, the comparison of IL-17 inhibitor netakimab with IL-6 receptor blocker tocilizumab and JAK inhibitor baricitinib in an observational study carried out in Moscow demonstrated a superior anti-inflammatory effect of both anti-cytokine drugs [31]. In this study, baricitinib had a less impressive result.

However, all three types of preemptive therapy were statistically significantly more effective than treatment without anti-inflammatory drugs, as in the COLORIT program. Nevertheless, it is impossible to make definite conclusions about the efficacy of IL-17 blockers and the feasibility of their use as a preemptive anti-inflammatory therapy in patients with moderate-to-severe COVID-19.

It seems that the correctly chosen indications determine the success of treatment rather than the type of anti-inflammatory drug and the mechanism of action. All patients hospitalized with moderate-to-severe COVID-19 require therapy including a combination of GCs and anticoagulants. Immediate preemptive anti-inflammatory therapy is required only if it is impossible to reverse the situation with persistent fever, asthenia, resistant CRP levels and an increase (or absence of a decrease) in the area of lung lesion in viral pneumonia.

Given the anti-inflammatory efficacy, JAK inhibitors should be preferred (ruxolitinib or baricitinib in our trials), then colchicine and IL-17 inhibitors with the least pronounced effect (secukinumab or netakimab). There is evidence in the literature about the efficacy of IL-6 receptor blockers (tocilizumab), although their effects became

statistically significant only in combination with GCs [32]. However, we should not forget about economic factors. If the cost of treatment of severe COVID-19 with colchicine is taken as a unit, the cost of treatment with IL-17 antagonists, JAK inhibitors, and tocilizumab will be 11–15, 18–20, and 24 times higher, respectively. It is hoped that new SARS-CoV-2 variants will be less likely to cause a cytokine storm. Given the vaccination and the appearance of new specific antiviral drugs, it will be possible to effectively treat patients with viremia. Such drugs include, for example, MIR-19, which interferes with a viral RNA in the cell, inhibits the ability to replicate, and is administered as inhalation [33]. Molnupiravir binds to SARS-CoV-2, induces RNA mutagenesis of viral RNA-dependent RNA polymerase (RdRp), and inhibits the ability of the virus to replicate [34]. Paxlovid (a combination of nirmatrelvir and ritonavir) is an antiviral drug that acts as an oral active inhibitor of 3CL protease involved in the activation of SARS-CoV-2 [35]. However, preemptive anti-inflammatory therapy will remain a necessary way to save patients with COVID-19, if the disease continues to progress.

Conclusions

1. In severe COVID-19 with viral pneumonia and the risk of a cytokine storm (persistent fever above 37.5 °C, asthenia, lymphopenia and elevated CRP by day 7–9 of the disease), preemptive anti-inflammatory therapy with ruxolitinib, colchicine, and secukinumab statistically significantly reduced the severity of inflammation, prevented the progression of the disease, and is accompanied by clinical improvement.
2. There were no statistically significant differences between the three drugs.

Limitations

The control group was selected on a case-control basis, and the comparison of the three drugs with the control was a case-control study.

The small number of patients in the groups should also be taken into account, which may not show statistically significant differences between anti-inflammatory drugs.

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