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# Coronavirus disease-2019 (COVID-19): value of IL-6 inhibitors

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic has drawn attention to new clinical and fundamental issues in the immunopathology of human diseases. Since in COVID-19 it is the ''hyperimmune'' response, called cytokine storm syndrome, which forms the basis of the pathogenesis of acute respiratory distress syndrome (ARDS) and multiorgan dysfunction in COVID-19, special attention is drawn to the possibility of "repurposing" (drug repurposing) of some widely used for treatment immune-mediated inflammatory rheumatic diseases (IMIRDs) anti-inflammatory drugs, including glucocorticoids (GC), disease-modified anti-rheumatic drugs (DMARDs), biologic agents and ''targeted'' DMARDs. In the spectrum of cytokines involved in the pathogenesis of cytokine storm syndrome in IMIRDs and COVID-19, great importance is attached to the pro-inflammatory cytokine, interleukin IL-6. The development and introduction into clinical practice of monoclonal antibodies (mAbs) that inhibit the activity of IL-6 are among the major advances in the treatment of IMIRDs, and in recent years, critical conditions within the framework of the cytokine storm syndrome, including in COVID-19. The review discusses the materials of numerous studies devoted to the problems of the efficacy and safety of mAbs to the IL-6 receptor (tocilizumab) and other mAbs that inhibit the activity of this cytokine in COVID-19. Despite the effectiveness of inhibiting IL-6 in patients with severe COVID-19, many theoretical and clinical problems of immunopathology and pharmacotherapy of this disease require further study.

**Key words:** COVID-19, immune-mediated inflammatory rheumatic diseases, interleukin 6, tocilizumab.

**Conflict of interests.** The author declares the absence of conflict of interests.

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# Коронавирусная болезнь-2019 (COVID-19): значение ингибиторов IL-6

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## Резюме

Пандемия коронавирусной болезни-2019 (COVID-19) привлекла внимание к новым клиническим и фундаментальным проблемам иммунопатологии заболеваний человека. Поскольку при COVID-19 именно гипериммунный ответ, получивший наименование синдром «цитокинового шторма», составляет основу патогенеза острого респираторного дистресс-синдрома и мультиорганной дисфункции при COVID-19. При этом особенно привлекательной является возможность репозиционирования (drug repurposing) некоторых широкоприменяемых для лечения иммуновоспалительных ревматических заболеваний (ИВРЗ) противовоспалительных лекарственных препаратов, включая глюкокортикостероиды, базисные противовоспалительные препараты, генно-инженерные биологические препараты и таргетные базисные противовоспалительные препараты. В спектре цитокинов, принимающих участие в патогенезе синдрома «цитокинового шторма» при ИВРЗ и COVID-19, большое значение придается провоспалительному цитокину интерлейкину (IL)-6. Разработка и внедрение в клиническую практику моноклональных антител (мАТ), ингибирующих активность IL-6, относится к числу крупных достижений в лечении ИВРЗ, а в последние годы – критических состояний в рамках синдрома «цитокинового шторма», в т. ч. при COVID-19. В обзоре обсуждаются материалы многочисленных исследований, посвященных проблемам эффективности и безопасности мАТ к рецептору IL-6 (тоцилизумаб) и других мАТ, ингибирующих активность этого цитокина при COVID-19. Несмотря на эффективность ингибирования IL-6 у пациентов с тяжелым течением COVID-19, требуется дальнейшее изучение многих теоретических и клинических проблем иммунопатологии и фармакотерапии этого заболевания.

**Ключевые слова:** COVID-19, иммуновоспалительные ревматические заболевания, интерлейкин-6, тоцилизумаб.

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The global pandemic of the Coronavirus Disease 2019 (COVID-19) [1, 2] has drawn attention to the novel clinical and fundamental issues of immune and pathological mechanisms of human diseases. The data that was accumulated during the research of pathogenic mechanisms of inflammatory rheumatic diseases (IRDs) can help us un-

derstand the nature of pathological processes that underly severe and potentially fatal complications of COVID-19. Advances in pharmacotherapy of IRD could improve the treatment of the novel coronavirus disease [3, 4]. The hyperimmune response, rather than the cytopathic effect of the virus alone, causes acute respiratory distress syndrome (ARDS) and multiple organ dysfunction in patients with COVID-19 [5]. So there is a promising possibility to repurpose some anti-inflammatory drugs that are widely used in rheumatology [6], including glucocorticoids (GCs), disease-modifying anti-rheumatic drugs (DMARDs), biologic agents, and targeted DMARDs [3, 4, 7].

The pathogenetic mechanisms of COVID-19 were summarized in several reviews [8, 9]. COVID-19 is caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus-2) that infects primarily type II pneumocytes and other cells expressing angiotensin-converting enzyme 2 (ACE II), which acts as the virus receptor. Replication of SARS-CoV-2 has a cytopathic effect on the target cells. The virus causes pyroptosis (a pro-inflammatory form of programmed cell death – apoptosis), which in turn induces the production of interleukin-1 (IL-1) and other pro-inflammatory cytokines by myeloid cells in the course of coordinated activation of innate and acquired immune responses. At the same time, SARS-CoV-2 suppresses the production of interferon (IFN) type I (IFN-α and IFN-β) and thereby weakens the antiviral immune response [10]. This promotes uncontrolled replication of the virus, and, as a consequence, the progression of the immune-inflammatory process that climaxes as the cytokine storm syndrome [11–14]. The clinical manifestations of the cytokine storm syndrome include primary and secondary hemophagocytic lymphohistiocytosis (HLH) [15], macrophage activation syndrome [16–18], and cytokine release syndrome as a complication of CAR-T-cell therapy (Chimeric Antigen Receptor T-Cell) of oncological disorders [19]. On the one hand, this syndrome is one of the most severe complications of some IRDs. On the other hand, it can be a consequence or stage of COVID-19 and manifests itself as ARDS, coagulopathy, and multiple organ dysfunction [20–22].

The pathogenetic basis of the cytokine storm syndrome is dysregulated production of a wide range of cytokines (both pro-inflammatory, immunoregulatory, and anti-inflammatory) and chemokines caused by the abnormal activation of innate and acquired immunity (Th1 and Th17 types). These substances include IL-1, IL-2, IL-6, IL-7, IL-8–10, IL-12, IL-17, IL-18, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), IFN-γ-inducible protein 10, monocyte chemotactic protein 1 (MCB1), macrophage inflammatory protein-1α (MBB1α), and chemokines (CCL1, CCL3, CCL5, CXCL8, CXCL9, CXCL10, and others). A pronounced increase in the concentration of these cytokines (to varying degrees and in different combinations) is characteristic of severe and especially of critical course of COVID-19 [23–26]. The immune abnormalities typical to the severe COVID-19 include profound lymphopenia, a decrease in the peripheral blood levels of $CD4^+$ T-cells, $CD8^+$ T-cells, T-regulatory cells, B-cells, monocytes, eosinophils, and basophils, overexpression of the exhaustion markers (NKGA2, and others) on the membrane of natural killer (NK) cells and $CD8^+$ T-cells. The peripheral blood tests identify biomarkers that indicate the activation of the Th17-type immune response, namely the expansion of pathogenic $CCR4^+$ $CCR6^+$ Th17-cells [27, 28], as well as T-cells that produce GM-CSF. The latter activates $CD14^+$ $CD16^+$ monocytes and induces the production of IL-6 and other pro-inflammatory mediators [29].

Interleukin-6 (IL-6) is considered to play a crucial role in the development of cytokine storm syndrome in patients with inflammatory rheumatic diseases (IRD) [30, 31] and COVID-19 [32, 33]. IL-6 is an autocrine, paracrine, and hormone-like regulator of various 'normal' and pathological biological processes (inflammation, metabolism, psychosomatic reactions, and others) (see the figure). Biological effects and molecular mechanisms of action of this cytokine are based on its ability to activate target genes that regulate differentiation, survival, apoptosis, and proliferation of various immune and non-immune cells in the human body [34–36]. Pleiotropism of IL-6 is mediated by a unique signaling system that includes IL-6 receptors (IL-6R) and downstream signal molecules. IL-6R consists of two subunits – an IL-6-binding chain (IL-6Rα) and a transmembrane signal-transducing receptor gp130 (130 kDa glycoprotein, IL-6Rβ). The membrane-bound IL-6Rα (mIL6Rα) is expressed by a limited range of cells (macrophages, neutrophils, CD4 T-cells, hepatocytes, podocytes, megakaryocytes, and specific intestinal epithelial cells). On the other hand, gp130 (IL-6Rβ) is present on almost all human cells. Binding of the IL-6-IL-6R complex to two gp130 proteins initiates the IL-6 signal cascade. Dimerization of gp130 induces activation of Janus kinases (JAK) 1 & 2 and phosphorylation of tyrosine residues in the cytoplasmic region of gp130. As noted above, most human cells do not express mIL-6R and are therefore resistant to the biological effects of IL-6. However, soluble (s) IL-6Rα can be found in the blood plasma and tissues. This soluble form is released during proteolysis of the membrane-bound form by $Zn^{2+}$ metalloproteinases ADAM (A Disintegrin and Metalloproteinase domain) 10 and 17. sIL-6-Pα protects IL-6 from enzymatic cleavage, increases its serum lifespan. Most importantly, sIL-6-Pα, in combination with IL-6, can bind to gp130 and activate cells that do not express mIL-6Pα. This process is called trans-signaling, while cell activation that is mediated by the interaction of IL-6 with mIL-6P is defined as classical (cis-) signaling. It is believed that trans-signaling mediates the pathogenic effects of IL-6 to a greater extent as compared to the classical signaling. At the same time, the classical signaling is also involved in the acute phase response, production of pathogenic Th17- and Th22-cells, and the suppression of T-regulatory cells. Recently, a new mechanism of IL-6 signaling has been characterized. It is called trans-presentation. IL-6 binds with IL-6Pα on the membrane of specific dendritic cells and is presented to the gp130 homodimer, which is expressed on the surface of adjacent T-cells. Researchers believe that this is how IL-6 induces the generation of a "pathogenic" subpopulation of Th17-cells [37].

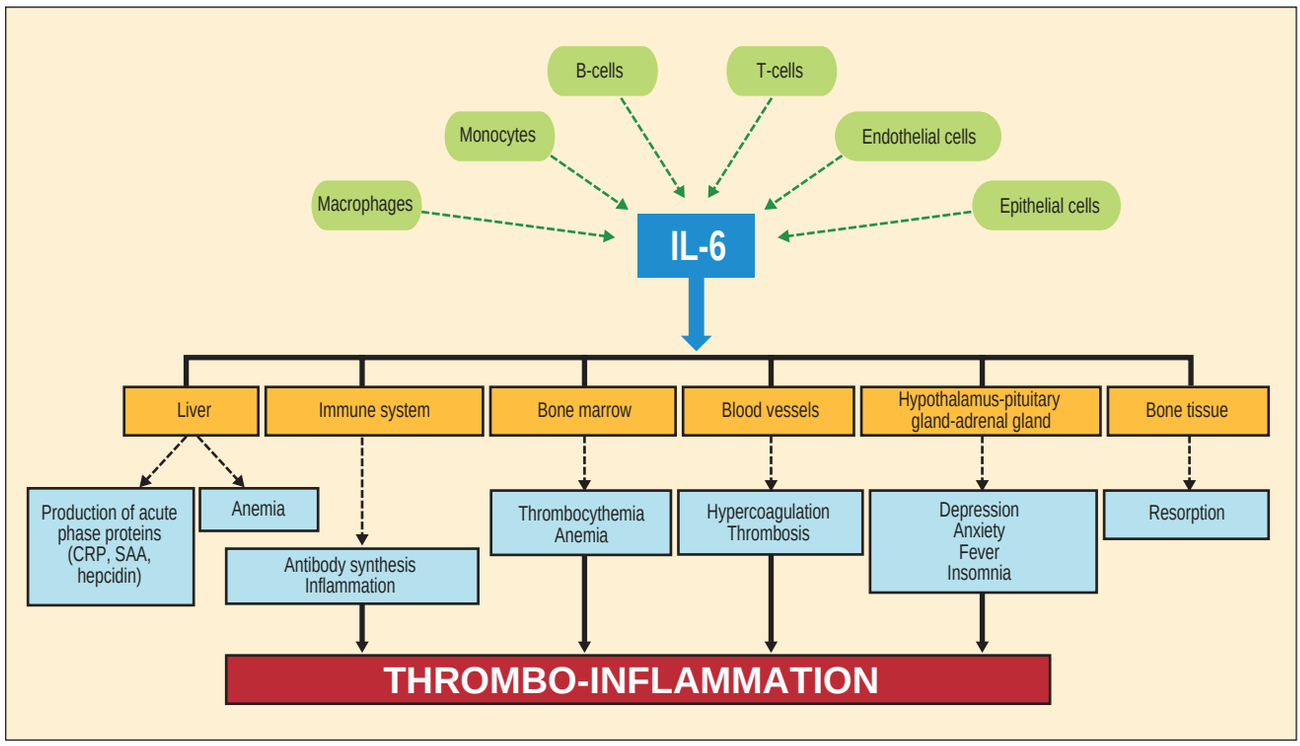


Figure. Main effects of interleukin-6
Note: CRP, C-reactive protein; SAA, Serum amyloid A protein.
Рисунок. Основные эффекты интерлейкина-6

The assumed important role of IL-6 in the immunopathogenesis of COVID-19 is supported by numerous studies that indicate an increase in the serum concentration of this cytokine in vivo [23, 38–40]. According to a meta-analysis, the level of IL-6 was 3 times higher in patients with severe COVID-19 ($n$ = 1,302) as compared to patients with mild/moderate disease ($p < 0.001$). The baseline concentration of IL-6 correlates with bilateral lung damage ($p = 0.001$) and the intensity of fever ($p = 0.001$) [41]. Another meta-analysis [42] ($n$ = 1,426 patients) showed that the mean baseline IL-6 concentration in severe COVID-19 was significantly higher than in non-severe COVID-19 ($p < 0.001$) and was significantly associated with increased mortality ($p = 0.03$). SARS-CoV-2 RNA (RNAmia) is detected in the serum of patients with severe COVID-19 pneumonia and is associated with a substantial increase in the IL-6 level [43]. This is consistent with the concept of viral sepsis as the leading cause of cytokine storm syndrome in COVID-19 [44].

One of the major advances in the treatment of IRDs [31, 35, 45–47] was the development and introduction into clinical practice of monoclonal antibodies (mAbs) that inhibit all IL-6 signaling pathways. In recent years, these drugs were approved for the treatment of critical conditions caused by the cytokine storm syndrome [48], including COVID-19 [39, 49, 50]. mAbs include (Table 1): tocilizumab (TCZ; Tocilizumab, Actemra, Roche, Switzerland), sarilumab (SAR; Sarilumab, Kevzara, Sanofi-Aventis, France) and, lately, siltuximab (SLT). A Russian drug, olokizumab (Artlegia, R-Pharm), has been registered for the treatment of RA recently. Olokizumab blocks IL-6, not IL-6R. A phase II randomized controlled trial of a Russian drug levilimab (BCD-089, BIOCAD) in RA is about to be completed. Levilimab is a human anti-IL-6R mAb. The IL-6 inhibitors have not been approved for use in COVID-19 yet, but these drugs (mainly TCZ) are used off-label to treat the most severe patients, often in a life-threatening condition.

## Tocilizumab

### Noncomparative studies (single arm) of Tocilizumab

The study by *P.Luo et al.* [51] included 15 patients. The TCZ doses varied from 80 to 600 mg (single intravenous injection). Three critically ill COVID-19 patients died on day 6 ($n$ = 2) and day 7 ($n$ = 1). The disease progressed in one patient. All other patients stabilized or improved, including three of the seven critical patients and all patients with moderate to severe disease. Notable, fatal outcome was associated with no positive changes in the concentration of CRP and IL-6. *X.Xu et al.* [52] presented a retrospective analysis of treating 21 patients with COVID-19 with TCZ. 18 patients received a single infusion of TCZ; three patients received two infusions within 12 hours. All patients showed normal body temperature, improved general symptoms, lesser need in mechanical ventilation (within 5 days in 75% of the patients), the disappearance of ground glass opacities on the CT-scans ($n$ = 19), normal lymphocyte and CRP levels (84.2%) one day after the TCZ infusion. On average, the patients were discharged from the hospital after 15.1 days. The authors concluded that the treatment with TCZ should be started as early

***Table 1***
***Comparative characteristics of IL-6 inhibitors***
***Таблица 1***
***Сравнительная характеристика ингибиторов IL-6***

| Characteristics | Tocilizumab | Sarilumab | Siltuximab |
|---|---|---|---|
| Antibody type | Humanized, IgG1 | Human, IgG1 | Humanized, IgG1κ |
| Therapeutic target | sIL-6R, mIL-6R | sIL-6R, mIL-6R | Circulating IL-6 |
| Suppression of the signaling | Cis-, trans-signaling | Cis-, trans-signaling | Cis-signaling |
| Mode of administration | Intravenous and subcutaneous | Subcutaneous | Intravenous |
| Standard dose | 8 mg/kg per month intravenously, 162 mg once a week subcutaneously | 150 or 200 mg subcutaneously once every 2 weeks | 11 mg/kg once every 3 weeks |
| Time of $C_{max}$ | 2,8 days after subcutaneous injection | 2 – 4 days after subcutaneous injection | No data available |
| Volume of distribution, L | 6,4 after subcutaneous injection | 8,3 after subcutaneous injection | 4.5 |
| Elimination half-life, days | ≤ 12 | ≤ 10 | 20.6 |
| Approved indications for use | Rheumatoid arthritis, systemic and polyarticular juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome induced by chimeric antigen receptor T-cell (CAR-T) therapy | Rheumatoid arthritis | Multicentric Castleman's disease (MCD) in patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative |

as possible if the disease progresses from moderate to severe, the patient shows ground glass opacities in the lungs and the increase in IL-6. *S.Scarscia et al.* [53] conducted a prospective multicenter study of TCZ, which included 63 patients with severe COVID-19. The administration of TCZ caused $PaO_2/FiO_2$ (oxygenation index) to change from 152 ± 52 to 283.73 ± 115.8 after 7 days and to 302.2 ± 126 after 14 days ($p < 0.05$). The overall mortality was 11% and was associated with high levels of basal D-dimer, but not IL-6. Initiation of TCZ therapy in the first 6 days after hospitalization increased the probability of survival (HR = 2.2; 95% CI: 1.3 – 6.7; $p < 0.05$).

The retrospective study by *R.Alattar et al.* [54] that included 25 patients with COVID-19 showed that TCZ treatment was associated with normalization of body temperature, a decrease in CRP level from 193 mg/L to less than 6 mg/L ($p = 0.0001$), and positive changes in lungs in 44% of the patients after 7 days and in 68% of the patients after 14 days. The number of patients on mechanical ventilation decreased from 84 to 60% after 7 days and to 28% after 16 days ($p = 0.001$). 9 (36%) patients were discharged, and three patients died during the follow-up period. *B.B.Uysal et al.* [55] noted a pronounced positive trend in 10 out of 12 patients with COVID-19 pneumonia after the infusion of TCZ. The positive effect was seen as normalization of the oxygen saturation (from 87.58 ± 3.12% to 94.42 ± 1%), body temperature, and CRP levels. The patients were discharged from the hospital within 18 days. *R.Marfella et al.* [56] found the patients with COVID-19 and hyperglycemia who received TCZ had significantly worse outcomes as compared to the patients with normoglycemia ($p < 0.009$). *V.Morena et al.* [57] assessed the efficacy of TCZ 51 patients with severe COVID-19 pneumonia (need for high nasal oxygen flow or mechanical ventilation, CRP > 40 mg/L; oxygen saturation < 93%). A significant decrease in the intensity of fever, CRP levels, and an increase in the level of lymphocytes was reported within 7 days after the intravenous infusion of TCZ ($p < 0.001$). After 34 days, 67% of the patients showed a decrease in the severity of pneumonia, 31 patients were discharged, 17 (33%) patients experienced deterioration, and 14 (27%) patients died. The risk of death was significantly higher in patients who needed mechanical ventilation at baseline (83.3%) as compared to the patients who needed the non-invasive oxygen support (20%) ($p = 0.0001$). The most common ADRs were an increase in the liver enzymes (29%), thrombocytopenia (14%), and fungal infection (27%). These data show the limited efficacy of TCZ in patients with a critical course of COVID-19 pneumonia who require mechanical ventilation and have a high risk of infectious complications. *P.Toniati et al.* [58] presented a prospective observation of 100 patients with COVID-19 and severe ARDS who needed mechanical ventilation: 43 patients received TCZ infusions in the ICU, and the remaining 57 received TCZ in the therapeutic department. 37 (65%) out of 57 patients showed improvement and switched to non-invasive ventilation, 7 remained stable, and 13 (23%) experienced a deterioration (10 patients died, three were transferred to the ICU). In the group of 43 ICU patients, 32 (74%) showed improvement (17 were weaned), two patients remained stable, and 10 died. Status of 77 (77%) patients improved or stabilized within 10 days. The ground glass opacities were no longer identified in the CT-scans of 66 of these patients. 15 patients recovered and were discharged from the


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clinic. The condition of 33 (33%) patients worsened. 20 of them died. According to *C.C.Price et al.* [59], patients with severe COVID-19 who were prescribed TCZ ($n$ = 153) had a higher survival rate (83%), equal to the survival rate (91%) in patients with the non-severe disease ($p$ = 0.11). 75% of the patients, who needed mechanical ventilation and received TCZ, survived. No severe ADRs were associated with TCZ.

## Comparative studies of Tocilizumab (as compared to the standard treatment)

*M.Roumier et al.* [64] administered TCZ to 30 patients with COVID-19 pneumonia and a rapid increase in pulmonary insufficiency. The comparison group included 29 patients. The groups were matched by the main demographic characteristics and severity of the disease. There was a decrease in the need for mechanical ventilation (odds ratio (OR) 0.42; 95% confidence interval (CI) 0.20–0.89; $p$ = 0.025), as well as mortality (OR 0.25; 95% CI 0.05 – 0.95; $p$ = 0.04) in the main group as compared to the control group after 8 days (6.0 – 9.75 days). The risk of subsequent transfer to the ICU decreased for the patients who did not need the intensive care at baseline (23 patients in the main group and 16 patients in the control group) (OR 0.17; 95% CI 0.06 – 0.48; $p$ = 0.0001). TCZ was tolerated well. Only one patient showed an increase in the hepatic enzymes, and one patient developed moderate pneumonia. A retrospective analysis of 111 patients was published. 42 received TCZ treatment, and 69 received standard therapy [65]. All patients in the TCZ group ($n$ = 42) received antiviral therapy, and 40% of them received GC. 62% of patients in the TCZ group were mechanically ventilated. Three patients died (on average, after 17.8 days of follow-up). 7 of 26 remained mechanically ventilated, and 17 of 26 developed a bacterial superinfection. No deaths or bacterial infections were reported in the standard therapy group. At the same time, the basal concentration of CRP, IL-6 ($p$ < 0.001), and neutrophils ($p$ = 0.04) was significantly higher in the TCZ group. The levels of lymphocytes ($p$ < 0.0001) were significantly lower in patients who were mechanically ventilated as compared to those who did not need it. An open-label case-control study included 86 patients. 21 of them received TCZ. It was found that TCZ was associated with a 75% reduction in the risk of death (RR 0.25; 95% CI 0.07 – 0.90) [66]. *E.C.Somers et al.* [67] studied the efficacy of TCZ in patients with COVID-19 who needed mechanical ventilation ($n$ = 78). The comparison group included 76 patients who did not receive this drug. The average duration of follow-up was 47 days (28 – 67 days). The risk of death reduced significantly in the TCZ group (RR 0.54; 95% CI 0.02 – 1.00). The mortality rate was 18% *vs* 36%, respectively ($p$ = 0.01). Important pieces of evidence of the efficacy of TCZ were an increase in the number of discharged patients (56% *vs* 40%; $p$ = 0.04) and a decrease in the number of patients who required mechanical ventilation during the follow-up period (18% *vs* 47%). At the same time, the TCZ group showed a 2-fold increase in the risk of superinfection (54% *vs* 26%; $p$ < 0.001), mostly in the form of ventilator-associated pneumonia (45% *vs* 20%; $p$ < 0.001). The pneumonia was associated with *Staphylococcus aureus* in most cases in both groups. Notably, the superinfection did not affect the mortality in the TCZ group (22% *vs* 15%; $p$ = 0.42). *R.Carpa et al.* [68] assessed the outcomes of COVID-19 pneumonia in 85 patients. 62 patients received TCZ in combination with the standard therapy (GC, lopinavir and ritonavir), and 23 patients received only the standard therapy. Administration TCZ (on average, in 4 days after the admission) led to a significant improvement in the survival as compared with the control group (HR 0.035; 95% CI 0.004 – 0.347; $p$ = 0.004), adjusted for the initial severity of the condition. 2 of 62 patients died in the TCZ group and 11 of 23 patients died in the control group. 92% and 42.1% of patients recovered (i.e., were discharged), respectively. Improvement of the lung function was noted in 64.8% of patients in the TCZ group who stayed in the hospital. All patients of the control group showed deterioration of the lung function and needed mechanical ventilation. No infectious complications were reported in both groups. *T.Klopfenstein et al.* [69] found a decrease in mortality and the need for transfer to the ICU in patients treated with TCZ ($n$ = 20) as compared to the control group ($n$ = 25) (25% *vs* 75%; $p$ = 0.002). Interestingly, the TCZ group included patients with more severe course of COVID-19, as was shown by the Charlson Comorbidity Index (5.3 *vs* 3.4; $p$ = 0.014), the oxygen therapy (13 L/min *vs* 6 L/min; $p$ < 0.001, lymphopenia (676/mm$^3$ *vs* 914/mm$^3$; $p$ = 0.037), and CRP levels (158 mg/L *vs* 105 mg/L; $p$ = 0.017). Recently, the results of a large observational study were reported. The study included 1,229 patients (10,673 patients/years) who were followed up in Spain. 260 (21%) patients received TCZ and 969 patients who did not receive TCZ [70]. The administration of TCZ to the patients with the baseline CRP levels over 150 mg/L was associated with a decrease in mortality (RR 0.38, 95% CI 0.16 – 0.72; $p$ = 0.005) and the combined outcome (need for transfer to ICU and mortality) (HR = 0.38, 95% CI 0.19 – 0.81; $p$ = 0.011). This trend was not confirmed for the patients with the baseline CRP levels below 150 mg/L. The propensity score matching in 21 patients with COVID-19 treated with TCZ and 21 patients on standard therapy was performed in the SMACORE study (SMAtteo COvid19 Registry) [71]. The preliminary analysis showed that TCZ does not reduce the need for transfer to ICU (OR = 0.11; 95% CI 0.00 – 3.38; $p$ = 0.22) and mortality within 7 days after drug infusion (OR = 0.78, 95% CI 0.06 – 9.34; $p$ = 0.84). *T.Kewan et al.* [72] conducted a retrospective analysis of the outcomes of 51 patients with COVID-19. 28 (55%) of the patients received TCZ treatment, and the rest received the standard therapy. Note that the patients on mechanical ventilation (regardless of the TCZ treatment) received systemic GC therapy (81% and 82%, respectively) and GC in combination with azithromycin (93% and 96%, respectively). Initially, the TCZ group included patients with a more severe condition as compared to the standard therapy group. So the TCZ group had a higher need for mechanical ventilation both at

baseline (68% *vs* 22%, respectively) and during the hospitalization (75% *vs* 48%, respectively). Nevertheless, the clinical state of the TCZ patients on mechanical ventilation improved faster (HR = 1.83, 95% CI 0.57 – 5.84) as compared to the control group. The clinical state of all TCZ patients also improved faster (HR = 1.14, 95% CI 0.55 – 2.38), regardless of the need for mechanical ventilation. The average duration of vasopressor therapy and mechanical ventilation was 2 days and 7 days in the TCZ group and 5 days and 10 days in the control group ($p = 0.039$ and $p = 0.11$, respectively). The incidence of infectious complications (18% and 22%) was similar. *R.M.Petrac et al.* [73] presented the results of a retrospective analysis of a multicenter study, which included 145 patients. 123 (84.8%) received one TCZ infusion, and 22 (15.2%) received 2 TCZ infusions. The overall mortality was 28.3%. At the same time, each additional day of delay in the administration of TCZ increased the risk of mechanical ventilation by 21% ($p = 0.002$) and did not depend on the use of GC ($p = 0.965$). The early administration of TCZ was associated with a decrease in mortality (13.5%) as compared to the later start of treatment (68.2%) ($p < 0.001$). The early administration of TCZ was also associated with a higher rate of discharge (59.5% *vs* 18.2%; $p < 0.001$). Late administration of TCZ was associated with a higher (17.8 times) mortality as compared to the early administration of the drug ($p < 0.001$). Thus, the early administration of TCZ reduced the need for mechanical ventilation and increased the possibility of recovery. Preliminary results indicate an improvement in lung damage during subcutaneous use of TCZ in patients with severe COVID-19 pneumonia ($n = 12$) and the absence of severe manifestations of cytokine storm syndrome [74]. The retrospective analysis of the TESERO (The Tocilizumab in Patients with Severe COVID-19 Pneumonia) study [75] is of great interest. This study enrolled 1351 patients with COVID-19, including 544 (40%) patients with severe COVID-19 pneumonia. All patients received the standard therapy (oxygen support, GC, azithromycin, antiviral therapy, low molecular weight heparin). 179 of 544 patients with COVID-19 pneumonia received TCZ (91 subcutaneously, 88 intravenously) in combination with the standard therapy, and 365 patients received the standard therapy only. Mechanical ventilation was initiated in 57 (16%) of 365 patients in the standard therapy group as compared to 33 (18%) of 179 patients who received TCZ ($p = 0.41$), regardless of the form of the drug (18% of those who received the intravenous injections and 19% of those who received the subcutaneous injections). Fatal outcomes were reported in 20% of patients in the standard therapy group and in 7% of patients who received TCZ ($p < 0.0001$). The mortality in the TCZ did not depend on the TCZ dosage form. It was 7% for the patients who received the intravenous injections and 8% for the patients who received the subcutaneous injections. TCZ was associated with a significant reduction in the mortality (RR = 0.61, 95% CI 0.40 – 0.92; $p = 0.02$) adjusted for gender, age, duration of symptoms, and the Subsequent Organ Failure Assessment Score (SOFA). However, the incidence of infectious complications in patients receiving TCZ (13%) was higher than in patients receiving standard therapy (4%) ($p < 0.0001$). *F.Perrone et al.* [76]. presented preliminary results of a prospective multicenter study TOCIVID-19 (phase IIa), which included 301 patients. 180 (59.8%) of them received TCZ (8 mg/kg, up to 800 mg). The null hypothesis said that mortality would be 20% (after 14 days) and 35% (after 30 days). TCZ decreased this outcome after 30 days (22.4%; $p < 0.001$), but not after 14 days (18.4%; $p = 0.52$). The efficacy of TCZ was higher in patients who did not require mechanical ventilation at baseline. *R.Rossotti et al.* [77] summarized the results of a retrospective analysis of the effectiveness of TCZ in 84 patients with COVID-19 (the majority of patients, 69.8%, were critically ill) in comparison with the control group ($n = 184$), who did not receive TCZ. The groups were matched by sex, age, severity, and comorbidities (Charlson Index). TCZ treatment was associated with improved survival (RR 0.499, 95% CI 0.262 – 0.952; $p = 0.035$), but longer hospital stay (HR 1.658, 95% CI 1.088 – 2.524, p = 0.019). The latter was primarily associated with the increased ADR rate. *L.M.Canziani et al.* [78] conducted a study that included 64 patients with COVID-19 who received TCZ. Another 64 patients were included in the control group. The mortality rate (27% and 38%, respectively) and the risk of death (RR 0.61, 95% CI 0.33 – 1.15) (within 30 days) did not differ between the groups. TCZ was associated with a decrease in the need for mechanical ventilation (RR 0.36, 95% CI 0.16 – 0.83, $p = 0.017$) and did not affect the risk of thrombosis, bleeding, and infection. *N. De Rossi et al.* [79] presented an analysis of a cohort study that included 158 patients with COVID-19 pneumonia at an early stage of pulmonary failure. 90 of these patients received TCZ (400 mg IV or 324 mg SC) along with the standard therapy. The mortality rate was 7.7% (7 out of 90 patients) in the TCZ group and 50% (34 out of 68 patients) in the comparison group. TCZ was associated with a significant reduction in the risk of death (HR: 0.057, 95% CI 0.017 – 0.0187), independent of the dosage form. Treatment with TCZ was not associated with infectious complications and other ADRs. *C.Campochiaro et al.* [80] assessed the outcomes of 65 patients with COVID-19 pneumonia. 32 of these patients received TCZ therapy. After 28 days, clinical improvement was noted in 69% of the TCZ patients and in 61% of the patients who received the standard therapy ($p = 0.61$). The mortality was 15% and 33%, respectively ($p = 0.15$). In the TCZ group, the predictor of mortality was older age, and the predictor of clinical improvement was a high basal $PaO_2/FiO_2$ ratio. The incidence of infectious complications did not differ between the groups (13% and 12%, respectively). *V.Carvalho et al.* [81] compared the efficacy of TCZ in 28 patients with severe COVID-19 who were in the ICU. Another 24 patients were enrolled in the control group. Despite the more severe condition at baseline (the need for GC, mechanical ventilation, a pronounced decrease in the gas exchange), there was no increase in mortality ($p = 0.3$) and the incidence of infectious complications in the TCZ group. On the contrary, CRP levels ($p = 0.009$), lymphocyte levels ($p = 0.02$), and lung function returned to normal

faster. *M.Mikulska et al.* [82] conducted an observational single-center study, which included 196 patients with severe COVID-19 pneumonia. 130 patients received anti-inflammatory therapy. 29 of them (22.3%) received TCZ (8 mg/kg, intravenously or 162 mg, subcutaneously), 45 (34.6%) received methylprednisolone (1 mg/kg for 5 days, intravenously) and 56 (43.1%) received TCZ and methylprednisolone (MP) in combination the with standard therapy. The other patients received the standard therapy only. It was found that the early prescription of TCZ (within 3 days after hospitalization) and/or MP was associated with 86.5% and 80.8% (after 14 and 30 days) survival rate as compared to the standard therapy (64.1%). This higher survival rate associated with a significant decrease in the risk of treatment failure (HR = 0.48, 95% CI 0.23 – 0.99, $p = 0.049$). A large observational study indicated the ineffectiveness of GC (as monotherapy or in combination with azithromycin) concerning mortality in patients with COVID-19 ($n = 2512$) [83]. The patients in the TCZ group ($n = 134$) showed a trend to a higher survival (HR 0.76, 95% CI 0.57 – 1.00) within 30 days – 46% as compared to 56% in the group of patients who did not receive TCZ. *N.Wadud et al.* [84] found that the survival rate of COVID-19 patients who received TCZ ($n = 44$) was significantly higher than in the control group ($n = 50$) (61.36% *vs* 48.0%, $p < 0.00001$). *G.Rojas-Marte et al.* [85] assessed mortality in 193 patients with COVID-19. 96 of these patients received TCZ, and 97 received the standard therapy. In general, the mortality rate did not differ between the groups (52% *vs* 62%, $p = 0.09$). However, TCZ patients who did not require mechanical ventilation showed lower mortality as compared to the control group (6% *vs* 27%, $p = 0.024$). A prospective study by *S.Ramino et al.* [86] enrolled 86 patients with COVID-19 who received TCZ and 86 patients in the control group. All patients received high doses of methylprednisolone (250 mg on the first day and 80 mg on days 2 – 5) and had clinical and laboratory signs of the cytokine storm syndrome. These signs included rapid progression of the respiratory failure and at least 2 out of 3 abnormal laboratory tests (an increase in the levels of CRP > 100 mg/L, ferritin > 900 μg/L, d-dimer > 150 μg/L). The indications for the use of TCZ (8 mg/kg, intravenously) were the progression of the lung function disorder within 2 days, despite the use of methylprednisolone. TCZ was associated with an increased likelihood of improved lung function and hospital discharge (RR 1.8, 95% CI 1.2 – 2.7) (on day 7), a 65% decrease in mortality (RR 0.35, 95% CI 0.19 – 0.65), and lesser need for mechanical ventilation (HR 0.29, 95% CI 0.14 – 0.65) as compared to the control group. The incidence of ADR was similar between the groups. The only exception was the increase in the incidence of pulmonary embolism in the TCZ group ($p = 0.0590$). *E.Moreno-Garcia et al.* [87] evaluated the use of TCZ in 77 patients with COVID-19 with ARDS in comparison with the control group ($n = 94$). TCZ treatment was associated with a decrease in the need for transfer to the ICU (10.3% *vs* 27.6%), $p = 0.005$), the need for mechanical ventilation (0 vs 13.8%, $p = 0.001$), as well as the combined outcome (transfer to the ICU and death) (OR 0.03, 95% CI 0.007 – 0.10, $p = 0.0001$).

## Meta-analyzes of Tocilizumab use

2 meta-analyzes [88, 89] summarized most of the above studies of the efficacy of TCZ in patients with COVID-19. A meta-analysis by *A.Kaye et al.* [88] included 9 comparative studies [64, 68, 69, 71, 75, 80, 83–85]. Overall, these studied enrolled 618 patients who received TCZ and 1,057 patients in the control group. The mortality rate was 26.1% in the TCZ group and 41.5% in the control group (OR 0.492, 95% CI 0.326 – 0.713, $p < 0.001$). The mortality rate among the patients treated with TCZ was 13.5% in 12 uncontrolled studies ($n = 803$) [51, 53–55, 57–61]. Another meta analysis [89] was based on the results of 13 retrospective [64–66, 68–70, 72, 75, 80, 83–85, 87] and 3 prospective studies [67, 71, 82], which included 2,488 patients who received the standard therapy and 1,153 patients who received TCZ. The mortality in the TCZ group (22.4%) was significantly lower than in the control group (26.21%) (OR 0.57, 95% CI 0.36 – 0.92, $p = 0.02$).

## Sarilumab and siltuximab

*E.Gremese et al.* [90] presented the data on SAR in 53 patients with severe COVID-19 pneumonia. 39 patients (66.7%) were administered SAR (1 infusion) in the therapeutic department, 14 patients (26.4%) were received it in the ICU (92.6% received 2 infusions). In the therapeutic department, 89.7% patients showed a significant clinical improvement (46.7% of the patients after 24 hours, 61.5% – after 3 days), 85.7% of patients no longer needed respiratory support, and 70.6% were discharged. 62.4% of those in the ICU were transferred to the therapeutic department, 35.8% remained in the ICU. The overall mortality rate was 5.7%, including 2.5% (1 patient) in the therapeutic department and 14.4% (2 patients) in the ICU. *E.Della-Torre et al.* [91] evaluated 28 patients with COVID-19 pneumonia who received SAR (400 mg, intravenous) and 28 patients in the comparison group. After 28 days, the clinical status improved in 61% of patients in the SAR group. The mortality rate was 7% in the SAR group. No significant differences were reported between the groups (64% and 18%, respectively) ($p > 0.05$). Predictors of clinical improvement in the SAR group were a basal $PaO_2/FiO_2$ ratio > 100 mm Hg and the lung lesion area < 17% in the CT-scan. Notably, the clinical status of patients with lung lesion area < 17% improvement faster (on average after 10 days) in the SAR group as compared to the standard therapy (on average after 24 days) ($p = 0.01$). *M.Benucci et al.* [92] noted an improvement in the lung function ($SpO_2/FiO_2$ ratio) in 7 out of 8 COVID-19 pneumonia patients treated with TCZ. The improvement was associated with an increase in lymphocyte levels and a decrease in the IL-6 and CRP concentrations. At the same time, preliminary results of a multicenter RCT (phase II / III) of SAR are disappointing. The study included 400 COVID-19 patients in a severe or

critical state (need for mechanical ventilation, high-speed nasal flow, and/or ICU) [93]. An interim analysis (within the phase II) did not reveal significant differences in the efficacy of SAR therapy at a dose of 400 mg intravenously ($n = 145$) as compared to the control group ($n = 77$) for all analyzed endpoints – mortality (23% *vs* 27%), the need for continued mechanical ventilation (23% *vs* 27%), clinical improvement (59% *vs* 41%), discontinuation of high-speed nasal flow procedures (58% *vs* 41%), and discharge (53% *vs* 41%). The exception was a more pronounced decrease in the concentration of CRP in the SAR group as compared to the control group (–79% *vs* –21%).

Preliminary results of the efficacy and safety of SLT in 21 patients with COVID-19 complicated by ARDS were reported [94]. In general, the efficacy is satisfactory. All patients showed normal CRP levels within 5 – 7 days. ⅔ patients showed improved or stable lung function. Nevertheless, the state of 5 patients worsened. All of them required mechanical ventilation, and one of them died.

## Conclusion

Numerous uncontrolled studies show the efficacy of IL-6 inhibitors in patients with severe COVID-19 pneumonia (with and without the cytokine storm). Nevertheless, the fundamental theoretical and clinical issues of immunopathology require further studies [95–97]. The most pressing issues are related to the true place of IL-6 in complex pathogenetic mechanisms that differ at different stages of this disease. Let us consider just a few of these issues. The serum levels of IL-6 in severe COVID-19 that is complicated by cytokine storm syndrome is significantly lower (from 7 to 627 pg/mL) [98–102] than in ARDS caused by other viral infections (578 – 1,618 pg/mL) [103–105]. The serum levels of IL-6 reached 10,000 pg/mL in patients with cytokine release syndrome caused by CAR-T-cell therapy [106]. The IL-6 level can exceed 50 pg/mL during active inflammation in patients with IRDs in the absence of ARDS and other manifestations of cytokine storm [107–110]. Moreover, the administration of recombinant human IL-6 to patients with cancer at a dose of 10 μg/kg to 20 μg/mL leads to a pronounced increase in the serum levels of IL-6 (> 4,000 pg/mL). However, it is not accompanied by severe lung damage or multiple organ failure [111]. This suggests that the development of COVID-19 pneumonia is associated with severe local inflammation (that may be dependent on IL-6), rather than with the systemic hyperimmune response characteristic of ARDS associated with other viral infections. On the other hand, there is evidence of the "protective" antiviral and antimicrobial effects of IL-6 in the early phase of infections [112]. This evidence is consistent with the numerous studies that showed an increased risk of infectious complications during the treatment of rheumatoid arthritis with TCZ and SAR [31, 34, 45–47]. The data of the RECOVERY study (Randomized Evaluation of COVid-19 thERapY) are important when considering the potential use of IL-6 inhibitors in the treatment of COVID-19. This study showed efficacy of dexamethasone therapy (6 mg per day for 10 days) in reducing mortality (within 28 days) in patients with COVID-19 ($n = 2,104$) who were mechanically ventilated (from 40% to 28%; $p = 0.0003$) or needed oxygen support (from 25% to 20%; $p = 0.0021$) as compared to the control group ($n = 4,321$). Notably, the higher efficacy of dexamethasone was not reported in patients who do not require oxygen support ($p = 0.14$) as compared to the control group [113]. These data can probably be extrapolated to other GCs and draw special attention to the negative results of RCTs (phase II / III) regarding the use of SAR in severe COVID-19 [93]. Preliminary results of the COVACTA RCT were presented. The TCZ treatment (as well as SAR) was not more effective than placebo in patients with severe COVID-19, as to most "primary" and "secondary" endpoints: improvement of clinical status ($p = 0.36$), mortality within 4 weeks (19.7% *vs* 19.4%; $p = 0.94$), the number of days without ventilation (22 days *vs* 16.5 days; $p = 0.320$) and the incidence of infectious complications (38.3% *vs* 40.6%) and severe infections (21.0% *vs* 25.9%). Although the time to discharge (or "readiness for discharge") was less (20 days) in the TCZ group than in the placebo group (28 days) ($p = 0.03$), these differences were not statistically significant [114]. From a clinical point of view, all these results are not conclusive regarding the choice of therapy in patients with COVID-19. However, they emphasize the heterogeneity of the pathogenic immune mechanisms of critical conditions as a manifestation of cytokine storm syndrome. In this regard, attention should be paid to the unique position of GCs in the control of inflammation. GCs block the synthesis of not only IL-6 but a wider range of pathogenetically important pro-inflammatory cytokines (including IL-1α/β, IL-12, IL -17, IFN-γ, TNF-α, and others) [115]. Overproduction of these cytokines is associated with a poor prognosis in COVID-19 pneumonia.

Suppression of hyperinflammation in COVID-19 (as in other immunoinflammatory diseases in humans) cannot be based on GC alone in the 21st century. Numerous studies aim to find new therapeutic targets for the development of personalized immunomodulatory therapy for COVID-19 [116, 117] based on the concept of "taxonomy" of cytokine-dependent diseases [7, 118]. Efficacy of inhibition of various pro-inflammatory cytokines, other than IL-6, is being studied (or discussed): IL-1 [119, 120], TNF-α [121], GM-CSF [122], IL-17 [123], IL-18 [124], cytotoxic terminal products of the complement system activation, etc. [125]. A promising area of immunopharmacotherapy for COVID-19 is associated with the repurposing of JAK (Janus kinase) inhibitors, primarily baricitinib (BARI). BARI is a targeted basic anti-inflammatory drug that is widely used to treat RA, and more recently, other immune-inflammatory diseases [126–128]. BARI inhibits the activity of JAK1 and JAK2 and thereby suppresses signaling of a wide range of pro-inflammatory cytokines, including IL-6 and GM-CSF. BARI also has an antiviral effect because it prevents infection of target cells with SARS-Cov-2 and intracellular assembly of the virus [129, 130] (Table 2).

In a short time, many scientific and clinical research studies were started and conducted to explore the issue of the cytokine storm syndrome in COVID-19. These studied dived into the abnormal immune mechanisms

*Table 2*
*Anti-inflammatory therapy for COVID-19*
*Таблица 2*
*Противовоспалительная терапия при COVID-19*

| Drugs | Mechanism | Use in COVID-19 | | Use in IRD |
|---|---|---|---|---|
| | | Advantages | Disadvantages | |
| Corticosteroids | Suppression of inflammation and immune response [115] | Decrease in mortality of COVID-19 patients on mechanical ventilation [113] | Slowing the virus RNA clearance [131] | RA, SLE, SS, SV, other inflammatory diseases |
| | | | Development of ADR [132] | |
| Aminoquinoline agents (chloroquine, hydroxychloroquine) | Moderate anti-inflammatory and immunosuppressive effect: production of IL-6 and TNF-α ↓ | Reduced viral load [133] | Efficacy was not proven; ADRs were reported [133] | RA, SLE, SS, SV, other IRDs |
| IL-6 inhibitors | Suppression of inflammation (see the text) | Reduced mortality | The efficacy was not confirmed in the RCT [113, 114], ADRs were reported (risk of infections, and others) | See Table 1 |
| IL-1 inhibitors | Suppression of inflammation [119] | Reduced mortality, improved lung function [120, 134 – 142] | The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.) | Autoinflammatory diseases [119]; sepsis [143], secondary HLH [144,145] and MAS [146] |
| Colchicine | Suppression of inflammation [147] | Effective against fever, skin lesions and myopericarditis [148,149] | The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.) | Autoinflammatory diseases, gouty arthritis [147] |
| Janus kinase inhibitors (baricitinib, ruxolitinib) | Suppression of inflammation [126,127], prevention of infection of lung cells with SARS-CoV-2 [128, 129] | Improvement in COVID-19 pneumonia [150–152] | The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.) | RA, PsA, UC, psoriasis, secondary HLH (ruxolitinib) [153–155] |
| Complement inhibitors<br>• mAb to C5a (eculizumab)<br>• Low molecular weight C3a inhibitor (AMI-101) | Suppression of complement-dependent inflammation [156] | Improvement in COVID-19 pneumonia [157, 158] | The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.) | Atypical HUS<br>Paroxysmal nocturnal hemoglobinuria<br>Myasthenia gravis<br>Optic neuromyelitis |
| GM-CSF inhibitors:<br>• mAb to GM-CSF | Suppression of inflammation [159] | Improvement in COVID-19 pneumonia [160–162] | The efficacy was not confirmed in the RCT, ADRs were reported (risk of infections, etc.) | RA (phase III) [163] |
| Intravenous immunoglobulin | Modulation of the immune response [164, 165] | Improvement in COVID-19 pneumonia [166, 167] | The efficacy was not confirmed in the RCT, ADRs were reported (acute lung damage, thrombosis) | IRD (off-label) |

Note: ADR, adverse drug reactions; RCT, randomized controlled trial; HUS, hemolytic uremic syndrome; RA, rheumatoid arthritis; PsA, psoriatic arthritis; UC, ulcerative colitis; SLE, systemic lupus erythematosus; SV, systemic vasculitis; SSS, systemic scleroderma; IIM, idiopathic inflammatory myopathies; HLH, hemophagocytic lymphohistiocytosis; IRDs, inflammatory rheumatic diseases.

and treatment of human immunoinflammatory diseases. One can hope that the efforts of scientists and physicians around the world will improve the prognosis for COVID-19, generate new knowledge for successful control of epidemics of viral infections that humanity may face in the future, and will improve the pharmacotherapy of widespread IRDs.

## References / Литература


1. Wu Z., McGoogan J.M. 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): 1239–1242. DOI: 10.1001/jama.2020.2648.
2. Wu F., Zhao S., Yu B. et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020; 579 (7798): 265–269. DOI: 10.1038/s41586-020-2008-3.
3. Nasonov E.L. [Coronavirus disease 2019 (COVID-19): a rheumatologist's thoughts]. *Nauchno-prakticheskaya revmatologiya*. 2020; 58 (2): 123–132. DOI: 10.14412/1995-4484-2020-123-132 (in Russian). / Насонов Е.Л. Коронавирусная болезнь 2019 (COVID-19): размышления ревматолога. *Научно-практическая ревматология*. 2020; 58 (2): 123–132. DOI: 10.14412/ 1995-4484-2020-123-132.
4. Schett G., Manger B., Simon D., Caporali R. COVID-19 revising inflammatory pathways of arthritis. *Nat. Rev. Rheumatol*. 2020; 16 (8): 465–470. DOI: 10.1038/s41584-020-0451-z.
5. Li G., Fan Y., Lai Y. et al. Coronavirus infections and immune responses. *J. Med. Virol*. 2020; 92 (4): 424–432. DOI: 10.1002/jmv.25685.
6. Kingsmore K.M., Grammer A.C, Lipsky P.E. Drug repurposing to improve treatment of rheumatic autoimmune inflammatory diseases. *Nat. Rev. Rheumatol*. 2020; 16 (1): 32–52. DOI: 10.1038/s41584-019-0337-0.
7. Schett G., Sticherling M., Neurath M.F. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat. Rev. Immunol*. 2020; 20 (5): 271–272. DOI: 10.1038/s41577-020-0312-7.
8. Tay M.Z., Poh C.M., Rénia L. et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nat. Rev. Immunol*. 2020; 20 (6): 363–374. DOI: 10.1038/s41577-020-0311-8.
9. Vabret N., Britton G.J., Gruber C. et al. Immunology of COVID-19: Current state of the science. *Immunity*. 2020; 52 (6): 910–941. DOI: 10.1016/j.immuni.2020.05.002.
10. Hadjadj J., Yatim N., Barnabei L. et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020; 369 (6504): 718–724. DOI: 10.1126/science.abc6027.
11. Mehta P. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020; 395 (10229): 1033–1034. DOI: 10.1016/S0140-6736(20)30628-0.
12. Pedersen S.F., Ho Y.C. A storm is raging. *J. Clin. Invest*. 2020; 130 (5): 2202–2205. DOI: 10.1172/JCI137647.
13. Henderson L.A., Canna S.W., Schulert G.S. et al. On the alert for cytokine storm: Immunopathology in COVID-19. *Arthritis Rheum*. 2020; 72 (7): 1059–1063. DOI: 10.1002/art.41285.
14. Moore J.B., June C.H. Cytokine release syndrome in severe COVID-19. *Science*. 2020; 368 (6490): 473–474. DOI: 10.1126/science.abb8925.
15. Ramos-Casals M., Brito-Zeron P., Lopez-Guillermo A. et al. Adult haemophagocytic syndrome. *Lancet*. 2014; 383 (9927): 1503–1516. DOI: 10.1016/S0140-6736(13)61048-X.
16. Carter S.J., Tattersall R.S., Ramanan A.V. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)*. 2019; 58 (1): 5–17. DOI: 10.1093/rheumatology/key006.
17. Crayne C.B., Albeituni S., Nichols K.E., Cron R.Q. The immunology of macrophage activation syndrome. *Front. Immunol*. 2019; 10: 119. DOI: 10.3389/fimmu.2019.00119.
18. Behrens E.M., Koretzky G.A. Review: Cytokine storm syndrome: looking toward the precision medicine era. *Arthritis Rheumatol*. 2017; 69 (6):1135–1143. DOI: 10.1002/art.40071.
19. Shimabukuro-Vornhagen A., Gödel P., Subklewe M. et al. Cytokine release syndrome. *J. Immunother. Cancer*. 2018; 6 (1): 56. DOI: 10.1186/s40425-018-0343-9.
20. Henry B.M., Vikse J., Benoit S. et al. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin. Chim. Acta*. 2020; 507: 167–173. DOI: 10.1016/j.cca.2020.04.027.
21. Connors J.M., Levy J.H. Thromboinflammation and the hypercoagulability of COVID-19. *J. Thromb. Haemost*. 2020; 18 (7):1559–1561. DOI: 10.1111/jth.14849.
22. Jose R.J., Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir. Med*. 2020; 8 (6): e46–47. DOI: 10.1016/S2213-2600(20)30216-2.
23. Huang C., Wang Y., Li X. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395 (10223): 497–506. DOI: 10.1016/S0140-6736(20)30183-5.
24. Chen N., Zhou M., Dong X. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet*. 2020; 395 (10223): 507–513. DOI: 10.1016/S0140-6736(20)30211-7.
25. Liu J., Li S., Liu J. et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*. 2020; 55: 102763. DOI: 10.1016/j.ebiom.2020.102763.
26. Wang J., Jiang M., Chen X., Montaner L.J. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J. Leukoc. Biol*. 2020; 108 (1): 17–41. DOI: 10.1002/JLB.3COVR0520-272R.
27. Xu Z., Shi L., Wang Y. et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med*. 2020; 8 (4): 420–422. DOI: 10.1016/S2213-2600(20)30076-X.
28. Pacha O., Sallman M.A., Evans S.E. COVID-19: a case for inhibiting IL-17? *Nat. Rev. Immunol*. 2020; 20 (6): 345–346. DOI: 10.1038/s41577-020-0328-z.
29. Zhou Y., Fu B., Zheng X. et al. Abberant pathogenic GM-CSF+T cells and inflammatory CD14+CD16+ monocyte in severe pulmonary syndrome patients of a new coronavirus. *bioRxiv* [Preprint. Posted: 2020, Feb. 20]. DOI: 10.1101/2020.02.12.945576.

30. Tanaka T., Narazaki M., Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy*. 2016;8 (8): 959–970. DOI: 10.2217/imt-2016-0.
31. Choy E.H., De Benedetti F., Takeuchi T. et al. Translating IL-6 biology into effective treatments. *Nat. Rev. Rheumatol*. 2020; 16 (6): 335–345. DOI: 10.1038/s41584-020-0419-z.
32. McGonagle D., Sharif K., O'Regan A., Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun. Rev*. 2020; 19 (6): 102537. DOI: 10.1016/j.autrev.2020.102537.
33. Zhang C., Wu Z., Li J.W. et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist. Tocilizumab may be the key to reduce the mortality. *Int. J. Antimicrob. Agents*. 2020; 55 (5): 105954. DOI: 10.1016/j.ijantimicag.2020.105954.
34. Calabrese L.H., Rose-John S. IL-6 biology: implications for clinical targeting in rheumatic disease. *Nat. Rev. Rheumatol*. 2014; 10 (12): 720–727. DOI: 10.1038/nrrheum.2014.127.
35. Nasonov E.L., Lila A.M. [Inhibition of interleukin 6 in immune inflammatory rheumatic diseases: achievements, prospects, and hopes]. *Nauchno-prakticheskaya revmatologiya*. 2017; 55 (6): 590–599. DOI: 10.14412/1995-4484-2017-590-599 (in Russian). / Насонов Е.Л., Лила А.М. Ингибиция интерлейкина 6 при иммуновоспалительных ревматических заболеваниях: достижения, перспективы и надежды. *Научно-практическая ревматология*. 2017; 55 (6): 590–599. DOI: 10.14412/1995-4484-2017-590-599.
36. Kang S., Tanaka T., Narazaki M., Kishimoto T. Targeting Interleukin-6 signaling in clinic. *Immunity*. 2019; 50 (4): 1007–1023. DOI: 10.1016/j.immuni.2019.03.026.
37. Heink S., Yogev N., Garbers C. et al. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells. *Nat. Immunol*. 2017; 18 (1): 74–85. DOI: 10.1038/ni.3632.
38. Tian W., Jiang W., Yao J. et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. *J. Med. Virol*. 2020; 92 (10):1875–1883. DOI: 10.1002/jmv.26050.
39. Nasonov E.L. [Immunopathology and immunopharmacotherapy of coranavirus disease 2019 (COVID-19): focus on interleukin 6]. *Nauchno-prakticheskaya revmatologiya*. 2020; 58 (3): 245–261. DOI: 10.14412/ 1995-4484-2020-245-261 (in Russian). / Насонов Е.Л. Иммунопатология и иммунофармакотерапия коронавирусной болезни 2019 (COVID-19): фокус на интерлейкин 6. *Научно-практическая ревматология*. 2020; 58 (3): 245–261. DOI: 10.14412/1995-4484-2020-245-261.
40. Henry B.M., de Oliveira M.H.S., Benoit S. et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin. Chem. Lab. Med*. 2020; 58 (7): 1021–1028. DOI: 10.1515/cclm-2020-0369.
41. Coomes E.A., Haghbayan H. Interleukin-6 in COVID-19: A systemic review and meta-analysis. *Rev. Med. Virol*. 2020; e2141. DOI: 10.1002/rmv.2141.
42. Aziz M., Fatima R., Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. *J. Med. Virol*. 2020: 92 (11): 2283–2285. DOI: 10.1002/jmv.25948.
43. Chen X., Zhao B., Qu Y. et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin. Infect. Dis*. 2020; ciaa449. DOI: 10.1093/cid/ciaa449.
44. Li H., Liu L., Zhang D. et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet*. 2020; 395 (10235): 1517–1520. DOI: 10.1016/S0140-6736(20)30920-X.
45. Nasonov E.L., ed. [Genetically engineered biologicals in the treatment of rheumatoid arthritis]. Moscow: IMA-PRESS; 2013 (in Russian). / Насонов Е.Л., ред. Генно-инженерные биологические препараты в лечении ревматоидного артрита. М.: ИМА-ПРЕСС; 2013.
46. Nasonov E.L. Use of tocilizumab for rheumatoid arthritis: new evidence. *Nauchno-prakticheskaya revmatologiya*. 2011; 49 (6): 46–56. DOI: 10.14412/1995-4484-2011-521 (in Russian). / Насонов Е.Л. Применение тоцилизумаба при ревматоидном артрите: новые данные. *Научно-практическая ревматология*. 2011; 49 (6): 46–56. DOI: 10.14412/1995-4484-2011-521.
47. Nasonov E.L., Lila A.M. The efficacy and safety of sarilumab, fully human monoclonal antibodies against interleukin 6 receptor, in rheumatoid arthritis: new evidence. *Nauchno-prakticheskaya revmatologiya*. 2019; 57 (5): 564–577. DOI: 10.14412/1995-4484-2019-564-57 (in Russian). / Насонов Е.Л., Лила А.М. Эффективность и безопасность сарилумаба (полностью человеческие моноклональные антитела к рецептору интерлейкина 6) при ревматоидном артрите: новые данные. *Научно-практическая ревматология*. 2019; 57 (5): 564–577. DOI: 10.14412/1995-4484-2019-564-57.
48. Koch C., Barrett D., Teachey T. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Exp. Rev. Clin. Immunol*. 2019; 15 (8): 813–822. DOI: 10.1080/1744666X.2019.1629904.
49. Liu B., Li M., Zhou Z. et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J. Autoimmun*. 2020; 10: 102452. DOI: 10.1016/j.jaut.2020.102452.
50. González-Gay M.A., Mayo J., Castañeda S. et al. Tocilizumab: from the rheumatology practice to the fight against COVID-19, a virus infection with multiple faces. *Expert Opin. Biol. Ther*. 2020; 20 (7): 717–723. DOI: 10.1080/14712598.2020.1770222.
51. Luo P., Liu Y., Qiu L. et al. Tocilizumab treatment in COVID-19: a single center experience. *J. Med. Virol*. 2020; 92 (7): 814–818. DOI: 10.1002/jmv.25801.
52. Xu X., Han M., Li T. et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc. Natl. Acad. Sci. USA*. 2020; 117 (20): 10970–10975. DOI: 10.1073/pnas.2005615117.
53. Sciascia S., Aprà F., Baffa A. et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19. *Clin. Exp. Rheumatol*. 2020; 38 (3): 529–532.
54. Alattar R., Ibrahim T.B.H, Shaar S.H. et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J. Med. Virol*. 2020: 92 (10): 2042–2049. DOI: 10.1002/jmv.25964.
55. Uysal B., Ikitimur H., Yavuzer S. et al. Tocilizumab challenge: A series of cytokine storm therapy experiences in hospitalized COVID-19 pneumonia patients. *J. Med. Virol*. 2020; 92 (11): 2648–2656. DOI: 10.1002/jmv.26111.

56. Marfella R., Paolisso P., Sardu C. et al. Negative impact of hyperglycaemia on tocilizumab therapy in COVID-19 patients. *Diabetes Metab*. [Preprint. Posted: 2020, May 21]. DOI: 10.1016/j.diabet.2020.05.005.
57. Morena V., Milazzo L., Oreni L. et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *Eur. J. Intern. Med*. 2020; 76: 36–42. DOI: 10.1016/j.ejim.2020.05.011.
58. Toniati P., Piva S., Cattalini M. et al. Brescia International Research and Training HUB (BIRTH). Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun. Rev*. 2020; 19 (7):102568. DOI: 10.1016/j.autrev.2020.102568.
59. Price C.C., Altice F.L., Shyr Y. et al. Tocilizumab treatment for cytokine release syndrome in hospitalized COVID-19 patients. *Chest* [Preprint. Posted: 2020, Jun. 15]. DOI: 10.1016/j.chest.2020.06.006.
60. Issa N., Dumery M., Guisset O. et al. Feasibility of tocilizumab in ICU patients with COVID-19. *J. Med. Virol*. [Preprint. Posted: 2020, Jun. 2]. DOI: 10.1002/jmv.26110.
61. Campins L., Boixeda R., Perez-Cordon L. et al. Early tocilizumab treatment could improve survival among COVID-19 patients. *Clin. Exp. Rheumatol*. 2020; 38 (3): 578.
62. Hassoun A., Thottacherry E.D., Muklewicz J. et al. Utilizing tocilizumab for the treatment of cytokine release syndrome in COVID-19. *J. Clin. Virol*. 2020; 128: 104443. DOI: 10.1016/j.jcv.2020.104443.
63. Alberici F., Delbarba E., Manenti C. et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int*. 2020; 97 (6): 1083–1088. DOI: 10.1016/j.kint.2020.04.002.
64. Roumier M., Paule R., Groh M. et al. Interleukin-6 blockade for severe COVID-19. *medRxiv* [Preprint. Posted: 2020, Apr. 22]. DOI: 10.1101/2020.04.20.20061861.
65. Quartuccio L., Sonaglia A., McGonagle D. et al. Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care. *medRxiv* [Preprint. Posted: 2020, May 10]. DOI: 10.1101/2020.05.01.20078360.
66. Ramaswamy M., Mannam P., Comer R. et al. Off-label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system: A Case-control study. *medRxiv* [Preprint. Posted: 2020, May 19]. DOI: 10.1101/2020.05.14.20099234.
67. Somers E.C., Eschenauer G.A., Troost J.P. et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clin. Infect. Dis.* 2020; ciaa954. DOI: 10.1093/cid/ciaa954.
68. Capra R., De Ross N., Mattioli F. et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur. J. Intern. Med*. 2020; 76: 31–35. DOI: 10.1016/j.ejim.2020.05.009.
69. Klopfenstein T., Zayet S., Lohse A. et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med. Mal. Infect.* 2020; 50 (5): 397–400. DOI: 10.1016/j.medmal.2020.05.001.
70. Martinez-Sanz J., Muriel A., Ron R. et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: A multicenter cohort study. *medRxiv* [Preprint. Posted: 2020, Jun. 09]. DOI: 10.1101/2020.06.08.20125245.
71. Colaneri M., Bogliolo L., Valsecchi P. et al. the COVID IRCCS San Matteo Pavia Task Force. Tocilizumab for treatment of severe COVID-19 patients: Preliminary results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms*. 2020; 8 (5): 695. DOI: 10.3390/microorganisms8050695.
72. Kewan T., Covut F., Al Jaghbeer M.J. et al. Tocilizumab for treatment of patients with severe COVID–19: A retrospective cohort study. *EClinicalMedicine*. 2020; 24: 100418. DOI: 10.1016/j.eclinm.2020.100418.
73. Petrak R., Skorodin N., Van Hise N. et al. Tocilizumab as a therapeutic agent for critically Ill patients infected with SARS-CoV-2. *medRxiv* [Preprint. Posted: 2020, Jun. 8]. DOI: 10.1101/2020.06.05.20122622.
74. Mastroianni A., Greco S., Apuzzo G. et al. Subcutaneous tocilizumab treatment in patients with severe COVID-19-related cytokine release syndrome: An observational cohort study. *EClinicalMedicine*. 2020; 24: 100410. DOI: 10.1016/j.eclinm.2020.100410.
75. Guaraldi G., Meschiari M., Cozzi-Lepri A. et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020; 2 (8): e474–484. DOI: 10.1016/S2665-9913(20)30173-9.
76. Perrone F., Piccirillo M.C., Ascierto P.A. et al. Tocilizumab for patients with COVID-19 pneumonia. The TOCIVID-19 prospective phase 2 trial. *medRxiv* [Preprint. Posted: 2020, Jul. 2]. DOI: 10.1101/2020.06.01.20119149.
77. Rossotti R., Travi G., Ughi N. et al. Safety and efficacy of anti-IL-6-receptor tocilizumab use on severe and critical patients affected by coronavirus disease 2019: a comparative analysis. *J. Infect.* 2020; 81 (4): e11–17. DOI: 10.1016/j.jinf.2020.07.008.
78. Canziani L.M., Trovati S., Brunetta E. et al. Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: A retrospective case-control survival analysis of 128 patients. *J. Autoimmun*. [Preprint. Posted: 2020, Jul. 8]. DOI: 10.1016/j.jaut.2020.102511.
79. De Rossi N., Scarpazza C., Filippini C. et al. Early use of low dose tocilizumab in patients with COVID-19: A retrospective cohort study with a complete follow-up. *EClinical Medicine*. 2020; 25: 100459. DOI: 10.1016/j.eclinm.2020.100459.
80. Campochiaro C., Della-Torre E., Cavalli G. et al. for the TOCI-RAF Study Group. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur. J. Intern. Med*. 2020; 76: 43–49. DOI: 10.1016/j.ejim.2020.05.021.
81. Carvalho V., Turon R., Goncalves B. et al. Effects of tocilizumab in critically ill Patients with COVID-19: A quasi-experimental study. *medRxiv* [Preprint. Posted: 2020, Jul. 15]. DOI: 10.1101/2020.07.13.20149328.
82. Mikulska M., Nicolini L.A., Signori A. et al. Tocilizumab and steroid treatment in patients with severe COVID-19 pneumonia. *medRxiv* [Preprint. Posted: 2020, Jun. 26]. DOI: 10.1101/2020.06.22.20133413.
83. Ip A., Berry D.A., Hansen E. et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients – An observational study. *medRxiv* [Preprint. Posted: 2020, May 25]. DOI: 10.1101/2020.05.21.20109207.

84. Wadud N., Ahmed N., Shergil M.M. et al. Improved survival outcome in SARs-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration. *medRxiv* [Preprint. Posted: 2020, May 16]. DOI: 10.1101/2020.05.13.20100081.
85. Rojas-Marte G.R., Khalid M., Mukhtar O. et al. Outcomes in patients with severe COVID-19 disease treated with tocilizumab – A case-controlled study. *QJM*. 2020; 113 (8): 546–550. DOI: 10.1093/qjmed/hcaa206.
86. Ramiro S., Mostard R.L.M., Magro-Checa C. 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. *Ann. Rheum. Dis*. 2020; 79 (9): 1143–1151. DOI: 10.1136/annrheumdis-2020- 218479.
87. Moreno Garcia E., Caballero V.R., Albiach L. et al. Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection. *medRxiv* [Preprint. Posted: 2020, May 16]. DOI: 10.1101/2020.06.05.20113738.
88. Kaye A.G., Siegel R. The efficacy of IL-6 inhibitor tocilizumab in reducing severe COVID-19 mortality: A systematic review. *medRxiv* [Preprint. Posted: 2020, Sep. 3]. DOI: 10.1101/2020.07.10.20150938.
89. Boregowda U., Perisetti A., Nanjappa A. et al. Addition of tocilizumab to the standard of care reduces mortality in severe COVID-19: A systematic review and meta-analysis. *medRxiv* [Preprint. Posted: 2020, Sep. 3]. DOI: 10.1101/2020.07.10.20150680.
90. Gremese E., Cingolani A., Bosello S.L. et al. Sarilumab use in severe SARS-CoV-2 pneumonia. *medRxiv* [Preprint. Posted: 2020, May 18]. DOI: 10.1101/2020.05.14.20094144.
91. Della-Torre E., Campochiaro C., Cavalli G. et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann. Rheum. Dis*. 2020; 79 (10): 1277–1285. DOI: 10.1136/annrheumdis-2020-218122.
92. Benucci M., Giannasi G., Cecchini P. et al. COVID-19 pneumonia treated with Sarilumab: A clinical series of eight patients. *J. Med. Virol*. [Preprint. Posted: 2020, May 30]. DOI: 10.1002/jmv.26062.
93. Regeneron/Sanofi. Regeneron and Sanofi Begin Global Kevzara (Sarilumab) clinical trial program in patients with severe COVID-19. Available at: *https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-begin-global-kevzarar-sarilumab-clinical*
94. Gritti G., Raimondi F., Ripamonti D. et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv* [Preprint. Posted: 2020, Jun. 20]. DOI: 10.1101/2020.04.01.20048561.
95. Sinha P., Matthay M.A., Calfee C.S. Is a ''cytokine storm'' relevant to COVID-19? *JAMA Intern. Med*. 2020; 180 (9): 1152–1154. DOI: 10.1001/jamainternmed.2020.3313.
96. Scherger S., Henao-Martinez A., Franco-Parades C., Shapiro L. Rethinking interleukin-6 blockade for treatment of COVID-19. *Med. Hypothesis*. 2020; 144: 110053. DOI: 101016/j.methy.2020.110553.
97. Jamilloux Y., Henry T., Belot A. et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun. Rev.* 2020; 19 (7): 102567. DOI: 10.1016/j.autrev.2020.102567.
98. Wu C., Chen X., Cai Y. et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern. Med*. 2020; 180 (7): 934–943. DOI: 10.1001/jamainternmed.2020.0994.
99. Qin C., Zhou L., Hu Z. et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin. Infect. Dis*. 2020; 71 (15): 762–768. DOI: 10.1093/cid/ciaa 248.
100. Zhou F., Yu T., Du R. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; 395 (10229): 1054–1062. DOI: 10.1016/S0140-6736(20)30 566-3.
101. Mo P., Xing Y., Xiao Y. et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin. Infect. Dis*. 2020; ciaa270. DOI: 10.1093/cid/ciaa270.
102. Cummings M.J., Baldwin M.R., Abrams D. et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020; 395 (10239): 1763–1770. DOI: 10.1016/S0140-6736(20)31189-2.
103. Calfee C.S., Delucchi K., Parsons P.E. et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir. Med*. 2014; 2 (8): 611–620. DOI: 10.1016/S2213-2600(14) 70097-9.
104. Famous K.R., Delucchi K., Ware L.B. et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am. J. Respir. Crit. Care Med*. 2017; 195 (3): 331–338. DOI: 10.1164/rccm. 201603-0645OC.
105. Sinha P., Delucchi K.L., Thompson B.T. et al. Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. *Intensive Care Med*. 2018; 44 (11): 1859–1869. DOI: 10.1007/s00134-018-5378-3.
106. Maude S., Barrett D.M. Current status of chimeric antigen receptor therapy for haematological malignancies. *Br. J. Haematol*. 2016; 172 (1): 11–22. DOI: 10.1111/bjh.13792.
107. Shimamoto K., Ito T., Ozaki Y. et al. Serum interleukin 6 before and after therapy with tocilizumab is a principal biomarker in patients with rheumatoid arthritis. *J. Rheumatol*. 2013; 40 (7): 1074–1081. DOI: 10.3899/jrheum.121389.
108. Diaz-Torne C., Ortiz M.D.A., Moya P. et al. The combination of IL-6 and its soluble receptor is associated with the response of rheumatoid arthritis patients to tocilizumab. *Semin. Arthritis Rheum*. 2018; 47 (6): 757–764. DOI: 10.1016/ j.semarthrit.2017.10.022.
109. Berti A., Cavalli G., Campochiaro C. et al. Interleukin-6 in ANCA-associated vasculitis: Rationale for successful treatment with tocilizumab. *Semin. Arthritis Rheum*. 2015; 45 (1): 48–54. DOI: 10.1016/j.semarthrit.2015.02.002.
110. Umare V., Nadkarni A., Nadkar M. et al. Do high sensitivity C-reactive protein and serum interleukin-6 levels correlate with disease activity in systemic lupus erythematosuspatients? *J. Postgrad. Med*. 2017; 63 (2): 92–95. DOI: 10.4103/0022-3859.188550.
111. van Gameren M.M., Willemse P.H., Mulder N.H. et al. Effects of recombinant human interleukin-6 in cancer patients: a phase I–II study. *Blood*. 1994; 84 (5): 1434–1441.
112. Velazquez-Salinas L., Verdugo-Rodriguez A., Rodriguez L.L., Borca M.V. The role of interleukin 6 during viral

infections. *Front. Microbiol*. 2019; 10: 1057. DOI: 10.3389/fmicb.2019.01057.
113. Horby P., Lim W.S., Emberson J.R. Dexamethasone in hospitalized patients with Covid-19 – Preliminary report. *New Engl. J. Med*. [Preprint. Posted: 2020, Jul. 17]. DOI: 10.1056/NEJMoa2021436.
114. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. Available at: *https://www.roche.com/investors/updates/inv-update-2020-07-29.htm*
115. Cain D.W., Cidlowski J.A. Immune regulation by glucocorticoids. *Nat. Rev. Immunol*. 2017; 17 (4): 233–247. DOI: 10.1038/nri.2017.1.
116. Ingraham N.E., Lotfi-Emran S., Thielen B.K. et al. Immunomodulation in COVID-19. *Lancet Respir. Med*. 2020; 8 (6): 544–546. DOI: 10.1016/S2213-2600(20)30226-5.
117. Lu L., Zhang H., Zhan M. et al. Preventing mortality in COVID-19 patients: which cytokine to target in a raging storm. *Front. Cell Develop. Biol*. 2020; 8: 677. DOI: 10.3389/fcell.2020.00677.
118. Schett G., Elewaut D., McInnes I.B. et al. How cytokine networks fuel inflammation: Toward a cytokine-based disease taxonomy. *Nat. Med*. 2013; 19 (7): 822–824. DOI: 10.1038/nm.3260.
119. Nasonov E.L. The role of interleukin 1 in the development of human diseases]. *Nauchno-prakticheskaya revmatologiya*. 2018; 56 (Suppl. 1): 19–27. DOI: 10.14412/ 1995-4484-2018-19-27 (in Russian). / Насонов Е.Л. Роль интерлейкина 1 в развитии заболеваний человека. *Научно-практическая ревматология*. 2018; 56 (Прил. 1): 19–27. DOI: 10.14412/1995-4484-2018-19-27.
120. van de Veerdonk F.L., Netea M.G. Blocking IL-1 to prevent respiratory failure in COVID-19. *Crit. Care*. 2020; 24 (1): 445. DOI: 10.1186/s13054-020-03166-0.
121. Feldmann M., Maini R.N., Woody J.N. et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet*. 2020; 395 (10234): 1407–1409. DOI: 10.1016/S0140-6736(20)30858-8.
122. Lang F.M., Lee K.M., Teijaro J.R. et al. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat. Rev. Immunol*. 2020; 20 (8): 507–514. DOI: 10.1038/s41577-020-0357-7.
123. Pacha O., Sallman M.A., Evans S.E. COVID-19: a case for inhibiting IL-17? *Nat. Rev. Immunol*. 2020; 20 (6): 345–346. DOI: 10.1038/s41577-020-0328-z.
124. McClain K.L., Allen C.E. Fire behind the fury: IL-18 and MAS. *Blood*. 2018; 131 (13): 1393–1394. DOI: 10.1182/blood-2018-02-828186.
125. Risitano A.M., Mastellos D.C., Huber-Lang M. et al. Complement as a target in COVID-19? *Nat. Rev. Immunol*. 2020; 20 (6): 343–344. DOI: 10.1038/s41577-020-0320-7.
126. Schwartz D.M., Kanno Y., Villarino A. et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat. Rev. Drug Discov*. 2017; 16 (12): 843–862. DOI: 10.1038/nrd.2017.201.
127. Nasonov E.L., Lila A.M. [Janus kinase inhibitors in immuno-inflammatory rheumatic diseases: new opportunities and prospects]. *Nauchno-prakticheskaya revmatologiya*. 2019; 57 (1): 8–16. DOI: 10.14412/1995-4484-2019-8-16 (in Russian). / Насонов Е.Л., Лила А.М. Ингибиторы Янус-киназ при иммуновоспалительных ревматических заболеваниях: новые возможности и перспективы. *Научно-практическая ревматология*. 2019; 57 (1): 8–16. DOI: 10.14412/ 1995-4484-2019-8-16.
128. Nasonov E.L., Lila A.M. [Baricitinib: new pharmacotherapy options for rheumatoid arthritis and other immune-mediated inflammatory rheumatic diseases]. *Nauchno-prakticheskaya revmatologiya*. 2020; 58 (3): 304–316. DOI: 10.14412/1995-4484-2020-304-316 (in Russian). / Насонов Е.Л., Лила А.М. Барицитиниб: новые возможности фармакотерапии ревматоидного артрита и других иммуновоспалительных ревматических заболеваний. *Научно-практическая ревматология*. 2020; 58 (3): 304–316. DOI: 10.14412/1995-4484-2020-304-316.
129. Richardson P., Griffin I., Tucker C. et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020; 395 (10223): e30–31. DOI: 10.1016/S0140-6736(20)30304-4.
130. Stebbing J., Phelan A., Griffin I. et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect. Dis*. 2020; 20 (4): 400–402. DOI: 10.1016/S1473-3099(20)30132-8.
131. Russell C.D., Millar J.E., Baillie J.K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020; 395 (10223): 473–475. DOI: 10.1016/S0140-6736(20)30317-2.
132. Oray M., Abu Samra K., Ebrahimiadib N. et al. Long-term side effects of glucocorticoids. *Expert Opin. Drug Saf*. 2016; 15 (4): 457–465. DOI: 10.1517/14740338.2016.1140743.
133. Meyerowitz E.A., Vannier A.G.L., Friesen M.G.N. et al. Rethinking the role of hydroxychloroquine in the treatment of COVID-19. *FASEB J*. 2020; 34 (5): 6027–6037. DOI: 10.1096/fj.202000919.
134. Aouba A., Baldolli A., Geffray L. et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann. Rheum. Dis*. 2020; 79 (10): 1381–1382. DOI: 10.1136/annrheumdis-2020-217706.
135. Cavalli G., De Luca G., Campochiaro C. et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020; 2 (6): e325–331. DOI: 10.1016/S2665-9913(20)30127-2.
136. Navarro-Millán I., Sattui S.E., Lakhanpal A. et al. Use of anakinra to prevent mechanical ventilation in severe COVID-19: A case series. *Arthritis Rheumatol*. [Preprint. Posted: 2020, Jun. 30]. DOI: 10.1002/art.41422.
137. Franzetti M., Pozzetti U., Carugati M. et al. Interleukin-1 receptor antagonist anakinra in association with remdesivir in severe coronavirus disease 2019: A case report. *Int. J. Infect. Dis*. 2020; 97: 215–218. DOI: 10.1016/j.ijid.2020. 05.050.
138. Dimopoulos G., de Mast Q., Markou N. et al. Favorable anakinra responses in severe covid-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell Host Microbe*. 2020; 28 (1): 117–123.e1. DOI: 10.1016/j.chom.2020.05.007.
139. Day J.W., Fox T.A., Halsey R. et al. Interleukin-1 blockade with Anakinra in acute leukaemia patients with severe COVID-19 pneumonia appears safe and may result in clinical improvement. *Br. J. Haematol*. 2020; 190 (2): e80–83. DOI: 10.1111/bjh.16873.

140. Pontali E., Volpi S., Antonucci G. et al. Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease. *J. Allergy Clin. Immunol*. 2020; 146 (1): 213–215. DOI: 10.1016/j.jaci.2020.05.002.
141. Huet T., Beaussier H., Voisin H. et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol.* 2020; 2 (7): e393–400. DOI: 10.1016/S2665-9913(20) 30164-8.
142. Cauchois R., Koubi M., Delarbre D. et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc. Natl. Acad. Sci. USA*. 2020; 117 (32): 18951–18953. DOI: 10.1073/pnas.2009017117.
143. Shakoory B., Carcillo J.A., Chatham W.W. et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. *Crit. Care Med*. 2016; 44 (2): 275–281. DOI: 10.1097/CCM.0000000000001402.
144. Eloseily E.M., Weiser P., Crayne C.B. et al. Benefit of Anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheum*. 2020; 72 (2): 326–334. DOI: 10.1002/art.41103.
145. Mehta P., Cron R.Q., Hartwell J. et al. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol*. 2020; 2 (6): e358–367. DOI: 10.1016/S2665-9913(20)30096-5.
146. Monteagudo L.A., Boothby A., Gertner E. Continuous intravenous Anakinra infusion to calm the cytokine storm in macrophage activation syndrome. *ACR Open Rheumatol*. 2020; 2 (5): 276–282. DOI: 10.1002/acr2.11135.
147. Alekberova Z.S., Nasonov E.L. [Prospects for using colchicine in medicine: new evidence]. *Nauchno-prakticheskaya revmatologiya*. 2020; 58 (2): 183–190. DOI: 10.14412/1995-4484-2020-183-190 (in Russian). / Алекберова З.С., Насонов Е.Л. Перспективы применения колхицина в медицине: новые данные. *Научно-практическая ревматология*. 2020; 58 (2): 183–190. DOI: 10.14412/1995-4484-2020-183-190.
148. Recalcati S., Piconi S., Franzetti M. et al. Colchicin treatment of COVID-19 presenting with cutaneous rash and myopericarditis. *Dermatol. Ther*. 2020; e13891. DOI: 10.1111/dth.13891.
149. Della-Torre E., Della-Torre F., Kusanovic M. et al. Treating COVID-19 with colchicine in community healthcare setting. *Clin. Immunol*. 2020; 217: 108490. DOI: 10.1016/j.clim.2020.108490.
150. Cantini F., Niccoli L., Matarrese D. et al. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J. Infect*. 2020; 81 (2): 318–356. DOI: 10.1016/j.jinf.2020. 04.017.
151. Cao Y., Wei J., Zou L. et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J. Allergy Clin. Immunol.* 2020; 146 (1): 137–146.e3. DOI: 10.1016/j.jaci.2020. 05.019.
152. La Rosée F., Bremer H.C., Gehrke I. et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia*. 2020; 34 (7): 1805–1815. DOI: 10.1038/s41375-020-0891-0.
153. Wang J., Wang Y., Wu L. et al. Ruxolitinib for refractory/relapsed hemophagocytic lymphohistiocytosis. *Haematologica*. 2019; 105 (5): e210–212. DOI: 10.3324/haematol.2019.222471.
154. Ahmed A., Merrill S.A., Alsawah F. et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol*. 2019; 6 (12): e630–637. DOI: 10.1016/S2352-3026(19)30156-5.
155. Goldsmith S.R., Saif Ur Rehman S., Shirai C.L. et al. Resolution of secondary hemophagocytic lymphohistiocytosis after treatment with the JAK1/2 inhibitor ruxolitinib. *Blood Adv*. 2019; 3 (23): 4131–4135. DOI: 10.1182/bloodadvances.2019000898.
156. Wong E.K.S., Kavanagh D. Diseases of complement dysregulation – an overview. *Semin. Immunopathol*. 2018; 40 (1): 49–64. DOI: 10.1007/s00281-017-0663-8.
157. Diurno F., Numis F.G., Porta G. et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur. Rev. Med. Pharmacol. Sci*. 2020; 24 (7): 4040–4047. DOI: 10.26355/eurrev_202004_20875.
158. Mastaglio S., Ruggeri A., Risitano A.M. et al. The first case of COVID-19 treated with the complement C3 inhibitor AMY-101. *Clin. Immunol*. 2020; 215: 108450. DOI: 10.1016/j.clim.2020.108450.
159. Hamilton J.A. GM-CSF in inflammation. *J. Exp. Med*. 2020; 217 (1): e20190945. DOI: 10.1084/jem.20190945.
160. Temesgen Z., Assi M., Vergidis P. et al. First clinical use of lenzilumab to neutralize GM-CSF in patients with severe COVID-19 pneumonia. *medRxiv* [Preprint. Posted: 2020, Jun. 14]. DOI: 10.1101/2020.06.08.20125369.
161. Melody M., Nelson J., Hastings J. et al. Case report: use of lenzilumab and tocilizumab for the treatment of coronavirus disease 2019. *Immunotherapy.* 2020; 12 (15): 1121–1126. DOI: 10.2217/imt-2020-0136.
162. De Luca G., Cavalli G., Campochiaro C. et al. GM-CSF blockade with marvilimumab in severe COVID-19 pneumonia ans systemiv hyperinflammation: a single-centre, prospective cphort study. *Lancet Rheumatol*. 2020; 2 (8): 3465–3473. DOI: 10.1016/S2665-9913(20)30170-3.
163. Crotti C., Agape E., Becciolini A. et al. Targeting granulocyte-monocyte colony-stimulating factor signaling in rheumatoid arthritis: Future prospects. *Drugs*. 2019; 79 (16): 1741–1755. DOI: 10.1007/s40265-019-01192-z.
164. Perez E.E., Orange J.S., Bonilla F. et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J. Allergy Clin. Immun*. 2017; 139 (3, Suppl.): S1–46. DOI: 10.1016/j.jaci.2016.09.023.
165. Nguyen A.A., Habiballah S.B., Platt C.D. et al. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! *Clin. Immunol.* 2020; 216: 108459. DOI: 10.1016/j.clim.2020.108459.
166. Xie Y., Cao S., Dong H. et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. *J. Infect*. 2020; 81 (2): 318–356. DOI: 10.1016/j.jinf.2020.03.044.
167. Cao W., Liu X., Bai T. et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect. Dis*. 2020; 7 (3): ofaa102. DOI: 10.1093/ofid/ofaa102.


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