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E. Nasonov, M. Samsonov

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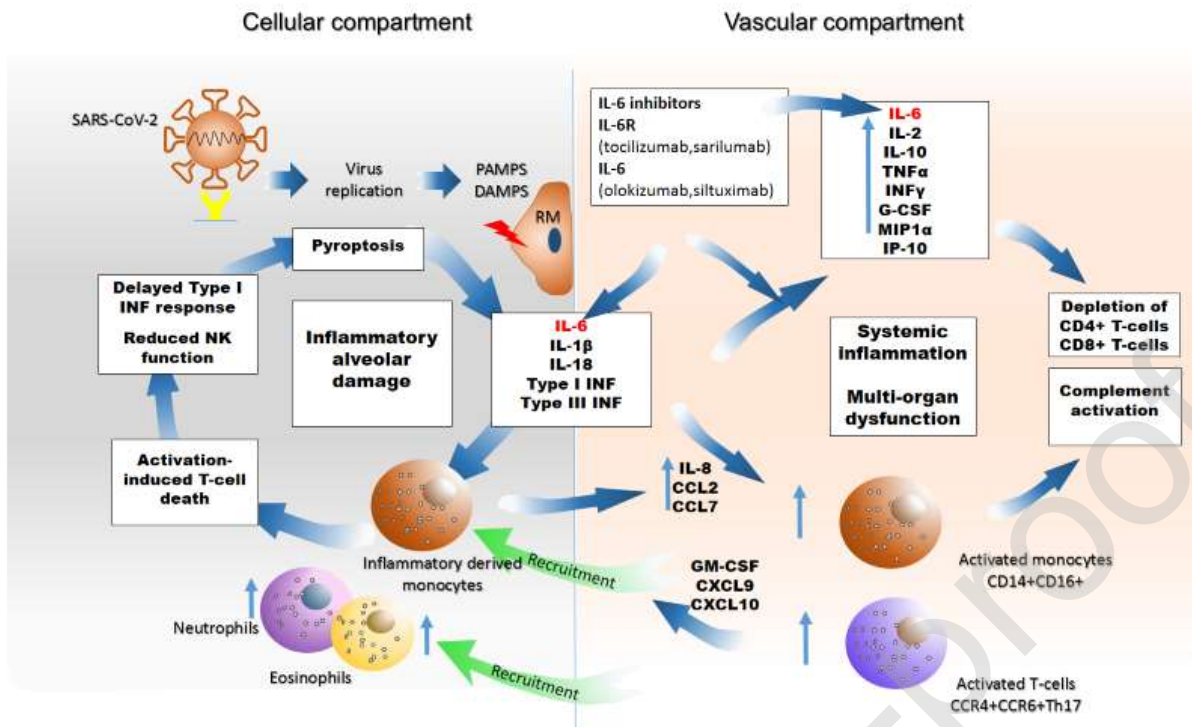
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The role of Interleukin 6 inhibitors in therapy of severe COVID-19.

E. Nasonov [1,2], M. Samsonov[3]

[1] V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia. [2] I.M. Sechenov First Moscow State Medical University, MOH, Moscow, Russia 1115522 Moscow, Kashirskoye roadway, 34A; 2119991 Moscow, Trubetskaya str, 8, bdg. 2; [3]RPharm JSC, Leninsky prospect 111, 11942, Moscow

Contacts: : Evgeny Nasonov; nasonov@irramn.ru[1] V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia. [2] I.M. Sechenov First Moscow State Medical University, MOH, Moscow, Russia 1115522 Moscow, Kashirskoye roadway, 34A; 2119991 Moscow, Trubetskaya str, 8, bdg. 2

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Graphical abstract

RM, Resident macrophages; INF, interferons; NK, natural killers; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor, TNFα, tumor necrosis factor alpha; IP-10, interferon (IFN)γ-induced protein 10; MIP1α, macrophage inflammatory protein; CCL2, CCL7, CXCL9, CXCL10, chemokines.

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Highlights

- Hyperimmune activation plays key role in severe COVID-19
- IL-6 increase associated with poor prognosis and progression
- IL-6 inhibition may improve patient's conditions
- Treat to target strategy may be applied in COVID-19

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1. Abstract

Cytokine storm syndrome (CSS) is a severe complication of inflammatory immune diseases or treatment of malignancies; it may also appear during the progression of COVID-19. CSS is caused by dysregulation of the synthesis of cytokines, including pro-inflammatory, regulatory, and anti-inflammatory cytokines and chemokines, leading to pathologic activation of innate and adaptive (Th1 and Th17 mediated) immunity. Interleukin-6 (IL-6) plays an important role in the pathogenesis of CSS. The significant role of IL-6 in pathogenesis of COVID-19 was confirmed in a range of studies, which showed that the plasma concentration of IL-6 was increased in patients with severe COVID-19. Currently, IL-6 inhibitor therapeutics are not yet approved for the treatment of COVID-19; however, these medicines, including tocilizumab (TCZ) are used off-label for the treatment of patients with severe COVID-19, including life-threatening conditions. The role of IL-6 in the pathogenesis of CSS during COVID-19 is important however, a number of related issues are not yet clear. These issues include the indications for treatment with IL-6 inhibitors, as well as the estimation of risk associated with the disease, outcomes, treatment options, and adverse drug reactions. The development of personalized immunomodulatory therapy, with respect to the role of cytokines in pathogenesis, requires the studies that aimed to find other relevant therapeutic targets for the treatment of CSS in patients with COVID-19. These therapeutic targets include inhibition of IL-1, IL-6, TNFα, GM-CSF, IFNγ, IL-17, IL-18, and also activation of the complement system.

The challenge of CSS in patients with COVID-19 is identifying the correct scientific targets and developing clinical trials aimed to evaluate the pathogenesis and treat immune-mediated inflammatory diseases (IMIDs). Hopefully, the significant efforts of scientists and physicians across the globe will improve the prognosis in COVID-19 patients and provide useful information on IMIDs required to support the struggle for treating potential viral outbreaks, and treatment of well-known IMIDs.

2. Introduction

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The 2019 Coronavirus Disease (COVID-19) and associated global pandemic [1,2] have drawn attention to new clinical and fundamental issues in the immunopathology of human diseases. The unique experience gained in the treatment of rheumatology patients and of studying the pathogenetic mechanisms and pharmacotherapy of immunoinflammatory rheumatic diseases (IMRD) is of great importance for deciphering the nature of the pathological processes underlying severe, potentially fatal complications of COVID-19 [3,4]

In COVID-19 patients, the hyperimmune response, rather than the action of the virus itself, contributes to the pathogenesis of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes [5]. Repurposing certain widely used immunomodulators [6], such as glucocorticoids (GC), disease-modifying anti-rheumatic drugs (DMARDs), and biologic drugs based on recombinant fusion proteins and targeted DMARDs [3,4,7] is a logical first step when faced with a new disease that caused a hyperimmune response.

The pathogenetic mechanisms of COVID-19 are summarized in a series of reviews [8,9]. Relevant to remind that SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus-2) is the established etiological factor of COVID-19, infecting primarily type II pneumocytes and other cells expressing angiotensin-converting enzyme (ACE) 2 protein, which is as a receptor and entry point for the virus. Replication of SARS-CoV-2 produces a cytopathic effect on target cells, causing their pyroptosis (pro-inflammatory form of programmed cell death -- apoptosis), therefore inducing synthesis of interleukin-1 (IL-1) and other proinflammatory cytokines by myeloid cells as part of innate immunity activation process. Noteworthy, along with the activation of immune cells, SARS-CoV-2 expresses proteins that inhibit the synthesis of type I Interferon (IFN) (IFNα and IFNß), thereby weakening antiviral immune responses and providing an optimal environment for rapid replication of the virus. Increasing of the viral load and enhancing viral cytopathic effects, results in the rapid progression of the immunoinflammatory process [10,11] leading to CSS [12-16]. Clinical manifestations of CSS include primary and secondary hemophagocytic lymphohistiocytosis [17], macrophage activation syndrome [18], and cytokine release syndrome as a complication of therapy with CAR T-cells (Chimeric Antigen Receptor T-Cells) [19].

The pathogenetic origin of CSS is associated with the dysregulated synthesis of a wide range of cytokines (pro-inflammatory, immunoregulatory, and anti-inflammatory) and chemokines, reflecting the pathological activation of innate and acquired (Th1 and Th17) immunity. These include IL-1, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-17, IL-18, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF)-α, interferon (IFN)γ-induced protein 10, monocyte chemoattractant

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protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, chemokines (CCL1, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) (Figure 1)

A significant increase in the concentration of these cytokines (in varying combinations and to various degrees) is characteristic of serious and especially severe forms of COVID-19 [20-24]. Common immunopathological manifestations of severe COVID-19 include severe lymphopenia, lower counts of CD4+ T cells, CD8+ T cells, B cells, natural killer (NK) cells, T-regulatory cells, monocytes, eosinophils, and basophils in peripheral blood [24-28]. Cytotoxic lymphocytes (NK cells, CD8+ T cells) are characterized by hyperexpression of «exhaustion» markers (NKGA2, etc.) [29]. Activation of the Th17-type immune response in severe COVID-19 is manifested by the expansion of pathogenic CCR4+CCR6+Th17 cells in the peripheral blood [25], as well as T cells synthesizing GM-CSF, which, by activating CD14+CD16+ monocytes, induces production of IL6 and other pro-inflammatory mediators [30]. Morphological examination of the lungs in COVID-19 patients reveals massive infiltration of mostly proinflammatory phenotype lymphocytes (CCR4+CCR6+Th17+CD4 T cells), neutrophils and macrophages, diffuse alveolar damage with deposition of hyaline membranes, fibrin thrombi, small vessel occlusions, and development of microinfarcts, and extravasation [31].

IL-6 seems to play a crucial role among all cytokines involved in the pathogenesis of CSS in IMIDs [32] and COVID-19 [15,33,34]. Introduction of monoclonal antibodies (mAbs) inhibiting this cytokine receptors with medicines such as Tocilizumab and Sarilumab, into clinical practice has been a major achievement in treating IMIDs [35,36], and in recent years – in the management of critically ill patients with CSS [32,37], including COVID-19 [33,38]. Data related to biological effects and molecular MOA of IL-6 are understood and are summarized in a number of published reviews [39,40]. IL-6 is known as a multifunctional (pleiotropic) cytokine, synthesized by immune and stromal cells in response to activation of toll-like receptors mediated by "molecular patterns" associated with pathogens and damage (pathogen-associated molecular patterns and damage-associated molecular patterns) (Figure 2).

The biological activity of IL-6 is determined by its potential to activate target genes that regulate cell differentiation, survival, proliferation, and apoptosis. IL6 functions as an autocrine, paracrine, and "hormone-like" regulator of various normal and pathological biological processes associated with local and systemic inflammation, metabolism, and tumorigenesis. Its pleiotropic properties are determined by a unique signaling system that includes IL-6 receptors (R) and

downstream signaling molecules. IL-6R consists of 2 chains: IL6-binding chain (IL6-Rα), and transmembrane protein gp130 (130 kDa glycoprotein) (IL6-Rß), which is a signal receptor. MIl-6Rα is expressed only in particular types of cells (macrophages, neutrophils, CD4 T cells, hepatocytes, podocytes, megakaryocytes, and specialized intestinal epithelial cells); while gp130 (IL6-Rß) is present in almost all cells of the human body. Initiation of the IL6-induced signaling cascade begins after binding of the IL-6 andIL-6-R complex to gp130, which, when dimerized, leads to activation of Janus kinases 1 and 2, via phosphorylation of tyrosine residues of the gp130 cytoplasmic site. Most human cells do not express mIl6-Rα, and therefore are resistant to the biological effects of IL6. However, the bloodstream and tissues also contain a soluble (s) form of IL6-Rα, which is formed by proteolytic cleavage mediated by Zn2+ metalloprotease ADAM (a Disintegrin and Metalloproteinase domain) 10 and 17, and, to a lesser extent, by "alternative splicing" of messenger RNA. SIl6-Rα protects IL-6 from enzymatic cleavage, and therefore, prolongs its circulation in the blood and, most importantly, in tandem with IL6, sIL-6Rα can bind to gp130, therefore activating many cell types that do not express mIL-6Rα. This process is called "trans-signaling", while cell activation mediated by the interaction of IL6 with mIl6-R is defined as cis-signaling. Hypothetically pathogenic effects of IL-6 are mostly determined by trans-signaling rather than cis-signaling. At the same time, "classical" (cis) signaling is also involved in the induction of acute-phase response, the production of pathogenic Th17 and Th22 cells, and suppression of T regulatory cells. Therefore, trans and cis-signaling provide a multidirectional contribution to the development of the immunopathological process in the course of disease progression. "Trans-presentation" as a new mechanism of IL-6 signaling has been described recently when IL6 binds to IL-6Rα on the membrane of specialized dendritic cells and is "presented" to the gp130 homodimer, expressed on the surface of cognate T cells. This mechanism is believed to play a major role in actualizing IL-6 potential to induce differentiation of pathogenic subpopulation of Th17 cells [41].

3. Interleukin 6 in COVID-19

IL-6 plays a crucial role in the immunopathogenesis of COVID-19 and is supported by data from numerous studies reporting increased serum concentrations of this cytokine, foremost in the severe cases [20,23,24,42-54]. A meta-analysis of COVID-19 cases (n=1302) indicates that the level of IL-6 was 3-fold higher in patients with severe vs mild/moderate COVID-19 (p <0.001), and that high baseline IL-6 concentration correlates with the development of bilateral lung damage

(p=0.001) and pyrexia (p=0.001) [55]. Other studies have shown that increasing IL-6 concentrations are associated with the progression of ARDS (p=0.03) and the risk of death [46]. According to another meta-analysis [56] (9 studies, 1426 patients), the average IL6 concentration in patients with severe COVID-19 was significantly higher than in non-severe cases (mean difference was 38.6 pg/ml; p<0.001). Meta-regression indicates that increased IL-6 concentrations were significantly associated with an increase in mortality (p=0.03). The risk of developing severe COVID-19 increases at IL-6 concentrations >55 pg/ml, and the risk of death at values >80 pg/ml. In critically ill COVID-19 patients, increased serum IL-6 concentrations correlate with the extent of inflammatory pulmonary involvement (>50%) following CT data, and a significant drop in CD4+ and CD8+ counts [49]. Data from T Herold et al. [54] shows that increased IL-6 concentration is significantly associated with the need for ventilatory support and the predicted development of respiratory failure (IL-6 > 80 pg/ml, AUC=0.98). While, generally, SARS-CoV-2 viral load does not correlate with the severity of COVID-19 [67], SARS-CoV-2 RNA is usually detected in the serum of critically ill COVID-19 patients (RNAemia) in combination with a marked increase in IL6 levels [57]. This is consistent with the concept of "viral sepsis" as the leading cause of CSS in COVID-19 [58].

4. Efficacy of anti-IL-6R and anti-IL-6 monoclonal antibodies in COVID-19

As already noted, mAbs blocking IL-6 binding to receptors (Tocilizumab, Sarilumab) or IL-6 (Siltuximab) are widely used in the treatment of IMIRDs [35]. A Phase II RCT of the original Russian human anti-IL-6R mAb (Levilimab, BCD-089, BIOCAD) in patients with rheumatoid arthritis is nearing completion. Olokizumab, in development by R-Pharm, blocks IL-6, not the IL-6 receptor, and has been approved for RA in Russia and is being evaluated in a global phase 3 RA program (NCT02760368, NCT02760407, NCT02760407, NCT03120949). Olokizumab is also being evaluated in a phase 2\3 randomized placebo control study for the treatment of COVID-19 (NCT04380519). IL-6 inhibitors are not yet approved for the treatment of COVID-19, however, anecdotal reports from physicians treating COVID-19 indicate the lifesaving potential of these drugs (primarily TCZ) based on number of non-placebo controlled or observational studies in patients with severe COVID-19 and ARDS (Table 1 and 2).

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Table 1. Characteristics of the uncontrolled trials evaluating Tocilizumab in COVID-19 patients.

Study	Type of study (Country)	Patients, n, (males, n or %)	Age, years (mean ± SD, or median with range	Comorbidities	Mortality ,%	Parameters that were associated with mortality
Luo et al. [59]	Retrospective (China)	15 (12)	73 (62-80)	Diabetes 26%, Hypertension 60%	20%	NS
Xu et al. [60]	Retrospective (China)	21 (18)	56.8±16.5 (25-88)	Hypertension 43%, Diabetes 24%, Cardiac 9.5%, COPD 4.8%	0%	NS
Sciasci et al. [61]	Prospective (Italy)	63 (56)	62.5±12	NA	11%	NS
Alattar et al. [62]	Retrospective (Qatar)	25 (23)	58 (50-63)	Diabetes 48% CKD 16% Cardiac 12%	12%	NS
Uysal et al. [63]	Retrospective (Turke)	12 (6)	65±11.3	Diabetes 58% Hypertension 58%	0%	NS
Gorgolas et al. [64]	Retrospective (Spain)	186 (91%)	65 (11.4)	Hypertension 50.5% Diabetes 21% Obese 30.6% COPD 7% CRF 3.2% Immunosuppresson 10.8%	19.3%	Age (<0.001) Comorbidity (0.003)
Morena et al. [66]	Retrospective (Italy)	51 (40)	60 (50-70)	Cardiac 49% Hypertension 29.4% Diabetes 11.9%	27%	NS
Toniati et al. [67]	Prospective (Italy)	100 (88)	62 (57-71)	Diabetes 17% Hypertension 46%	20%	NS

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				CKD 11% COPD 9%		
Price et al. [68]	Retrospective (USA)	153 (53%)	64 (median)	Diabetes 38% Lung 38% Hypertension 60% Obese 48%	13.1%	NS
Sinha et al. [69]	Observational (USA)	255 (161)	57 (47-70)	Obese 52.9% COPD 5.9% Diabetes 31% Hypertension 49% CKD 4.7%	10.9%	NS
Jordan et al. [70]	Retrospective (USA)	27 (23)	63 (median)	Hypertension 44& Diabetes 14% Cardiac 26% Pulmonary 33#	7.4%	NS
Campins et al. [72]	Prospective (Spain)				13.8%	NS
Hassoun et al. [73]	Retrospective (USA)	9 (6)	60 (37-88)	Diabetes 11% Hypertension 44% Cardiac 11% Obese 33%	22%	NS
Sanchez-Montalva et al. [74]	Vall d`Hebron prospective cohort (Spain)	82 (52)	59.1±19.8	Diabetes (19.5%) Immunosupression 12.2% Hypertension 23.5% Cardiac 6.1% COPD 7.3% ILD 2.4%)	26.8%	Age (p<0.001) Hypertension (0.001) Chronic renal failure (0.005) Charlson index (<0.001)
Fomina et al. [75]	Prospective (Russia)	89 (53)	<50 (32) 50-69 (51) 70> (14)	Hypertension 33% Diabetes 11% Lung 7% Obese 26%	12.3%	MV, Increased CRP level (>30 mg/L), reduced lymphocytes count (< 1000)
Pomponio et al. [76]	Phase II, pilot)	46 (33)	67.5 (34-89)	Hypertension 63% Diabetes 11%	15.2%	High IL-6 level (p=0.02)

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	(Italy)			CHF 4%		
Alberrici et al. [77]	Retrospective (Italy)	20 (16)	59 (51-64)	Renal transplant patients	25%	NS

SD – standard deviation; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease; MV- mechanical ventilation; NS – Not specified

Table 2. Characteristics of the controlled investigations evaluating Tocilizumab in COVID-19 patients.

Study	Type of study (Country)	Total patients (length of observation)	TCZ, n (males)	TCZ, Age, years (mean ± SD, or median with range	TCZ, mortality (%)	SOC, n (males)	SOC, Age, years (mean ± SD, or median with range	SOC, mortality (%)
Roumier et al. [78]	Retrospective, case control (France)	59 (median 8 days)	30 (24)	58.8 (12.4)	3	29 (24)	71.2 (15.4)	9
Quartuccio et al. [79]	Retrospective (Italy)	111 (NS)	42 (33)	62.4±11.8	9.5	69 (44)	56.2±14.2	0
Ramaswamy et al. [80]	Retrospective (USA)	86 (NS)	21 (13)	63.3 (15.6)	3	65 (36)	63.8 (15.9)	8
Somers et al. [81]	Prospective (USA)	154 (28 days)	78 (42)	55±14.9	18	76 (40)	60±14.5	36
Carpa et al. [82]	Retrospective (Italy)	85 (NS)	62 (45)	63 (54-73)	2	23 (19)	70 (55-80)	11
Klopfenstein et al. [83]	Retrospective, case control (France)	45 (until death and/or ICI admission)	20 (NA)	76.8±11	25	25 (NA)	70.7±15	48
Colaneri et al. [85]	Prospective (Italy)	112 (7 days)	21 (19)	NS	5	91 (63)	NS	19
Kewan et al. [86]	Retrospective cohort (USA)	51 (NS)	28 (20)	62 (53-71)	3	23 (11)	70 (55-75)	2

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Guaraldi et al. [89]	Retrospective cohort (Spain)	544 (45 (until death, discharge or mechanical ventilation)	179 (127)	64 (54-72)	13	365 (232)	69 (57-78)	20
Canziani et al. [92]	Retrospective cohort (Italy)	128 (NS)	64 (47)	63 (12)	27	64 (47)	64 (8)	38
De Rossi et al. [93]	Retrospective cohort (Italy)	158 (NS)	90 (64)	62.9 (12.5)	7.7%	90 (49)	71 (14.6)	50
Campochiaro et al. [94]	Retrospective (Italy)	65 (28 days)	32 (29)	64 (53-75)	15	33 (27)	60 (55-75.5)	33
Mikulska et al. [96]	Prospective cohort (Spain)	95 (NS)	29 (24)	65.9 (1-.2)	6	66 (41)	73.5 (13.4)	22
Wadud et al. [98]	Retrospective, case control (USA)	94 (until death or discharge)	44 (NS)	55.5	17	50 (NA)	66	26
Rojas-Marte et al. [99]	Retrospective, case control (USA)	193 (NS)	96 (74)	58.8 (13.6)	44.8	97 (63)	62.0	56.7
Ramiro et al. [100]	Prospective (Netherland)	172 (NS)	86 (68)	67 (12)	16.2	86 (68)	67 (11)	47.6
Moreno Carcis et al. [101]	Retrospective	171 (NS)	77 (53)	61.5 (12.4)	8	94 (59)	61.4 (16)	17
Kimming et al. [102]	Retrospective (USA)	111(62)	34 (78)	64.4±14/21	39.6	63 (28)	62.02±15.96	17.4

SD – standard deviation; NS – Not specified; SOC – standard of care.

Tocilizumab

A total of 15 patients were included in the study of Luo et al [59]. The patients received tocilizumab (TCZ) in the dose range from 80 to 600 mg (IV, single dose). 3 patients with a severe form of COVID-19 died on study Day 6 (n=2) and Day 7 (n=1); another patient showed the signs of disease progression. The remaining three out of seven patients were in critical condition, showed stabilization or clinical improvement. It is worth noting that fatal outcomes were associated with the absence of changes in CRP (C-reactive protein) and IL-6 levels. The mortality was associated with a lack of positive changes in the concentration of CRP and IL-6. Xu et al [60] performed a retrospective analysis of the results of TCZ treatment in 21 patients with COVID-19. A total of 18 patients received a single infusion of TCZ, 3 patients received 2 infusions within 12 hours. In the first day after the infusion of TCZ, normalization of body temperature, relief of symptoms, reduced need for mechanical lung ventilation (mechanical ventilation) and within 5 days,75% of the patients had elimination of ground-glass opacities on computer tomography (CT) scans (n=19), and normalization of lymphocytes and C-reactive protein (CRP) levels (84,2%) were observed. The mean duration of hospitalization was 15 days. The authors suggest that the treatment with TCZ should be initiated as soon as possible in cases where patients progress from moderate disease to severe disease or if there is detection of ground-glass opacities or increased IL-6 levels.

Scarscia et al. [61] conducted a prospective multicenter trial of TCZ in 63 patients with severe COVID-19. Treatment with TCZ led to positive changes in PaO2/FiO2 (oxygenation index) from 152±52 to 283,73±115,8 on day 7 and to 302,2±126 on day 14 of the study (p<0.05). The mortality rate was 11%; fatal outcomes were associated with higher levels of D-dimer rather than IL-6. Initiation of therapy with TCZ within the first 6 days of hospitalization was associated with increased survival rate: the hazard ratio (HR) was 2.2; 95% CI: 1,3–6,7; p<0.05.

A Retrospective study of Alattar et al [62] showed in 25 patients with COVID-19 the treatment with TCZ was associated with normalization of body temperature, reduced CRP levels (p=0.0001), improvements on CT in 44% and in 68% of patients on day 7 and day 14 respectively. The number of patients who needed mechanical ventilation was reduced from 84% to 60% on day 7 and to 28% on day 16 (p=0.001). During the follow-up period, 9 (36%) patients were discharged from the hospital; 3 patients died.

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Uysal et al [63] reported improvements in 10 of 12 COVID-19 patients after infusions with TCZ. These improvements include normalization of oxygen saturation levels (from 87.58±3.12% to 94.42±1%), body temperature, and CRP levels. All patients were discharged from hospitals within 18 days.

Gorgolas et al. [64] analyzed the outcomes of therapy with TCZ for 186 COVID-19 patients; 169 (91%) patients received a single infusion of TCZ, 16 patients received 2 infusions and 1 patient received 3 infusions. The majority of these patients (95.7%) were treated with methylprednisolone (250 mg once daily during the three days before infusion with TCZ). On day 15, fatal outcomes were reported for 36 patients; these outcomes were associated with older age (P<0.001), comorbidities (89% vs 63%, p=0.003), high IL-6 levels (p<0.001), high CRP levels (p<0.009), lymphopenia (p=0.001), or increased concentration of D-dimer (p=0.027). Early initiation of therapy with TCZ (patients with FiO2≤0.5%) was associated with better outcomes (assessed by the need for mechanical ventilation and mortality rates), as compared with later initiation of TCZ-based therapy patients with FiO2 >0.5%, (13% vs 37%, p<0.001). Severe adverse drug reactions related to TCZ were noted in 11 (59%) patients; infections (as a complication of the main disease) were reported in 13 (6.3%) patients. According to Marfella et al. [65], during treatment with TCZ in COVID-19 patients, hyperglycemia is associated with higher risk as compared to the patients with normal blood glucose levels (P<0.009).

The efficacy of treatment with TCZ in 51 patients with severe COVID-19 (including the need for mechanical ventilation, CRP level > 40 mg/L; oxygen saturation <93%) is discussed in the article of Morena et al. [66]. On day 7, after intravenous injection of TCZ, reduced fever, lower CRP levels, and elevated lymphocyte count were observed (p<0.001). On day 34, reduction in the severity of pneumonia symptoms was noted in 67% of patients; 31 patients were discharged from the hospital, 17 (33%) patients showed exacerbation of the main disease, and 14 (27%) patients died. The risk of death was significantly higher in mechanically ventilated patients with COVID-19 (83.3%) as compared to patients without mechanical ventilation (20%) (p=0.0001). The most frequent adverse drug reactions include elevated liver enzymes (29%), thrombocytopenia (14%), and fungal infections (27%). These data suggest that TCZ has limited efficacy in mechanically ventilated patients with severe COVID-19 which have a high risk of infections with other pathogens besides SARS-CoV 2.

Toniati et al. [67] described the results of a prospective study in 100 patients with COVID-19 and severe ARDS who needed mechanical ventilation. 43 patients received TCZ infusions in Intensive Care Units (ICUs), while the remaining 57 received TCZ in the Internal Medicine

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Department; clinical improvements allowed switching to non-invasive mechanical lung ventilation were noted in 37 (65%) of these patients, 7 patients had stable disease; exacerbation of the disease was noted in 13 (23%) patients (10 patients died, 3 patients were sent to ICUs). In the group of 43 patients who were in ICUs, clinical improvements were observed in 32 (74%) patients; (mechanical lung ventilation was stopped in 17 patients), the medical condition of 2 patients was stable; 10 patients died. In general, within 10 days, clinical improvement or stabilization was observed in 77 (77%) patients; in 66 patients obvious signs of recovery on CT scans were noted, such as the absence of ground glass opacities in the lungs; 15 patients fully recovered and were discharged from the hospital. Exacerbations of the main disease were reported in 33 (33%) patients; 20 patients died.

According to Price et al [68], the treatment with TCZ (п=153) in patients with severe COVID-19 was associated with improved survival rate (83%), similar to that in patients with non-severe COVID-19: 91%, p=0.11. In mechanically ventilated patients who received TCZ, the survival rate was 75%. The treatment with TCZ was not associated with severe adverse drug reactions (ADRs).

P Sinha et al [69] investigated certain IL-6 inhibitors, TCZ or SAR in 255 patients with severe COVID-19. There were 2 groups of patients based on the severity of the disease: those requiring ≤ 45% fraction of inspired oxygen (FiO2) (stage IIB) and > 45% FiO2 (stage III). The mortality rate in patients with IIB stage of the disease was lower than for patients in stage III (Adjusted Hazard Ratio, aHR = 0.24; 95% CI 0.08-0.74). Generally, 85.5% patients were discharged from the hospital. In addition, the patients with stage IIB disease had a higher recovery rate (aHR 1.43;95%CI 1.06-1.93) and reduced the need for mechanical ventilation (HR 0,43; 95%CI 0.24-0.79).

Jordan et al. [70] administered TCZ (400 mg, IV, single dose) to 27 patients with severe pneumonia caused by COVID-19. After the treatment, a significant reduction in fever, CRP levels, the need for oxygen supply, and the use of vasopressors were observed. A total of 16 of 24 mechanically ventilated patients were successfully extubated. However, in 3 of 4 patients without normalization of CRP levels, themedical condition deteriorated. The mortality rate was 7.4%.

Issa et al. [71] reported the results of therapy with TCZ (8 mg/kg) in 10 patients with severe COVID-19. These patients had laboratory abnormalities typical for CSS (7 patients were mechanically ventilated). Rapid normalization of laboratory parameters, including CRP, fibrinogen, D-dimer, ferritin) was observed in the majority of patients and associated with clinical

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improvements. On day 4 after the infusion, only 1 patient required mechanical ventilation; 1 death due to lung embolization.

Campis et al. [72] summarized the results of therapy with TCZ in 58 patients with severe COVID-19. During the follow-up period, the mortality rate was 13.8% (8 patients). A total of 57 (98.3%) patients received IV infusions with glucocorticosteroids: before treatment with TCZ (38.6%), simultaneously with TCZ (54.4%) and after infusion (7%). Reduced mortality rates were observed in patients who received glucocorticosteroids before TCZ (9.1%). In a small group of patients (n=9) with severe COVID-19 (5 mechanically ventilated who received TCZ 400-800 mg IV or 162 mg, subcutaneously), 2 patients died [73].

In the study of Sanchez-Montalva et al [74], 82 patients received treatment with TCZ. Respiratory failure and ARDS were observed in 62 (75.6%) and 45 (54.9%) patients, respectively; 34 (41.5%) patients were discharged from the hospital, 14 (17.1%) patients were sent to ICUs; there were 22 fatal outcomes (26.8%). Relatively high mortality rate can be explained by the late initiation of the treatment with TCZ:after the onset of ARDS (HR: 3.3; 95% CI 1.38-8.5), HR (corrected by age) was 2.1 (95% CI 0.8-5.8). There was no correlation between IL-6 levels and mortality (p=0.92). Adverse drug reactions typical for TCZ were not observed.

In a Russian clinical study [75], 89 patients with COVID-19 received TCZ. Mechanical ventilation was provided for 17 (19%) of these patients; the remaining patients received supplemental oxygen. During the follow-up period, 11 patients died; mechanical ventilation was provided for 10 of these patients.

In an open-label, pilot study of Pomponio et al [76] (n=46), treatment with TCZ led to significant clinical improvements in 46% of the COVID-19 patients with interstitial pneumonia; 11 patients died; mechanical ventilation was required for 11 patients. The effect of the study treatment correlated with high values of PaO2/FiO2 (p=0.008) and reductions in IL-6 level after infusion with TCZ (p=0.049).

In a study of M. Roumier et al [78], TCZ was used for the treatment of 30 patients with COVID-19 with rapid deterioration of medical conditions leading to lung failure. The control group included 29 patients; the treatment groups were well balanced on the main demographic parameters and severity of the disease. At day 8 (6,0–9,75 days), a reduced need for mechanical ventilation was observed in the TCZ group, as compared with the control group (OR: 0,42; 95% CI 0,20–0,89; p=0.025). The mortality rate was also lower in the TCZ group (OR: 0,25; 95% CI 05–0,95; p=0.04). Among the patients who were not sent to the ICU (23 patients in TCZ group and 16 patients in the control group), the reduced frequency of subsequent visits to ICU was noted

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(OR: 0.17; 95% CI 0.06–0,48; p=0.0001). In general, TCZ was well tolerated. An increase in liver enzymes has been observed in 1 patient; moderate pneumonia was observed in another patient.

A retrospective analysis was performed for the sample of 111 patients; 42 received TCZ (40% patients in combination with glucocorticosteroids); 69 patients received the standard treatment [79].

In the TCZ group, 62% of patients were on mechanical ventilation, three patients died (on average, within 17.8 days of observation), 7 of 26 remained on mechanical ventilation, and 17 of 26 developed bacterial superinfection. No deaths or bacterial infections were observed in the standard therapy group. The open-label case-control study included 86 patients, of whom 21 received TCZ. The treatment with TCZ was associated with a 75% reduction in the risk of mortality (HR: 0.25; 95% CI 0.07-0.90) [80].

Somers et al. [81] compared the efficacy of TCZ in 78 patients with COVID-19 who needed mechanical ventilation (n = 78); 76 patients were included in the control group. The mean duration of follow-up was 47 days (28-67 days). Patients treated with TCZ had a significant reduction in mortality risk (HR: 0.54; 95% CI 0.029-1.00). The mortality rate in the compared groups was 18% vs 36%, respectively (p = 0.01). In the TCZ group, there was an increase in the number of patients discharged from the hospital (56% vs 40%; p = 0.04), as well as a smaller number of patients requiring mechanical ventilation (18% vs 47%). At the same time, TCZ-treated patients had a 2-fold increase in the risk of superinfection (54% vs 26%; p <0.001), mainly ventilator-associated pneumonia (45% vs 20%; P <0.001), associated in most cases with Staphylococcus aureus. Noteworthy that in the group of patients receiving TCZ, the development of superinfection was not associated with a higher mortality rate (22% vs 15%; p = 0.42).

Carpa et al. [82] assessed the outcomes of COVID-19 pneumonia in 85 patients, among whom 62 patients received TCZ treatment and 23 patients received only standard therapy. TCZ treatment (on average, 4 days after admission to the hospital) resulted in a significant improvement in patients' survival compared to the control group (HR: 0.035; 95% CI 0.004-0.347; p = 0.004), adjusted for the initial severity of the medical condition. Fatal outcomes occurred in 2 of 62 patients in the TCZ group and 11 of 23 patients in the control group, and recovery (discharge from the hospital) occurred in 92% and 42.1% of patients, respectively. Lung recovery was noted in 64.8% of patients in the TCZ group who continued treatment in the hospital, while in the control group all patients showed deterioration in lung function, which required mechanical ventilation. The development of infectious complications was not observed in both treatment groups.

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Klopfenstein et al. [83] noted a decrease in mortality rates and the need for transfer to the ICU in patients treated with TCZ (n = 20), as compared with the control group (n = 25) (25% vs 75%; p = 0.002), despite the higher severity of COVID-19 in TCZ group: Charlson comorbidity index (5.3 vs 3.4; p = 0.014), intensity of oxygen therapy (13 L/min vs 6 L/min; p <0.001, lymphopenia (676/mm3 vs 914/mm3; p = 0.037) and CRP concentration (158 mg/L vs 105 mg/L; p = 0.017).

Recently, the results of a large observational study were presented, including 1229 patients (10673 patients/years), followed in clinics in Spain, 260 (21%) of which received TCZ treatment compared with 969 patients who did not receive TCZ treatment [84]. In the subgroup of patients with an initial increase in CRP concentration> 150 mg/L, the treatment with TCZ was associated with a decrease in mortality rate (IRR: 0.38, 95% CI 0.16-0.72; p = 0.005) as well as in combined parameter (the need for transfer to ICU + mortality rate) (IRR: 0.38, 95% CI 0.19-0.81; p = 0.011). However, in patients with the initial concentration of CRP <150 mg/L, there was no such correlation.

Treatment outcomes (propensity score) observed in the SMACORE study (SMAtteo Covid19 Registry) [85] were compared between the treatment groups: 21 patients who received TCZ treatment and 21 patients who were on standard therapy. The treatment with TCZ did not lead to reduced need for transfer to the ICU (OR: 0.11; 95% CI 0.00-3.38; p = 0.22) or reduced mortality rate within 7 days after infusion of the study drug (OR: 0.78, 95% CI 0.06-9.34; p = 0.84).

Kewan et al [86] conducted a retrospective analysis of outcomes in 51 patients with COVID-19, of whom 28 (55%) received TCZ treatment and the rest received standard therapy. It should be noted that patients on mechanical ventilation (regardless of TCZ treatment) received therapy with systemic glucocorticosteroids (GC) (81% and 82%, respectively). Initially, the severity of the main disease was higher in the TCZ group than the standard therapy group, which manifested in a higher need for mechanical ventilation, both at baseline (68% vs 22%, respectively) and during hospitalization (75% vs 48%, respectively). Nevertheless, in patients on mechanical ventilation, TCZ treatment led to an improvement in clinical condition faster (HR = 1.83, 95% CI 0.57-5.84) than in the control group, regardless of the need for mechanical ventilation. (HR = 1.14, 95% CI 0.55-2.38, respectively). In the TCZ group, the mean duration of vasopressor therapy was 2 days, and the mean duration of mechanical ventilation was 7 days; in the control group, these values were 5 days (p = 0.039) and 10 days (p = 0.11), respectively. The incidence of infectious complications was similar in both groups: 18% and 22%, respectively.

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Petrac et al. [87] presented the results of a retrospective analysis of a multicenter study, which included 145 patients, among whom 123 (84.8%) received one TCZ infusion, and 22 (15.2%) received 2 TCZ infusions. The overall mortality rate was 28.3%. Each additional day of delay in the initiation of treatment with TCZ increased the need for mechanical ventilation by 21% (p = 0.002) and did not depend on the use of glucocorticosteroids (p = 0.965). Early initiation of treatment with TCZ was associated with a decrease in mortality (13.5%), as compared to the patients who started the study treatment at a later time (68.2%) (p <0.001). Early initiation of treatment with TCZ was also associated with a higher rate of hospital discharge (59.5% vs 18.2%; p <0.001). In patients with late initiation of treatment with TCZ, the mortality rate was 17.8 times higher than in patients who started the TCZ treatment early (p <0.001). Thus, early initiation of treatment with TCZ reduced the need for mechanical ventilation and increased the chances of recovery. Preliminary results showed improvements in lung damage during treatment with subcutaneous TCZ in patients with severe COVID-19 pneumonia (n = 12) [88].

Retrospective analysis of the TESERO study (Tocilizumab in Patients with Severe COVID-19 Pneumonia) [89] included 1351 patients with COVID-19; 544 (40%) of these patients had severe COVID-19 pneumonia. All patients received standard therapy (oxygen supply, glucocorticosteroids (GC), azithromycin, antiviral therapy, low-weight heparin). Among 544 patients with COVID-19 pneumonia, 179 received TCZ treatment (91 subcutaneously, 88 intravenously), in combination with standard therapy, and 365 patients received standard therapy only. Switching to mechanical ventilation was required in 57 (16%) of 365 patients on standard therapy and in 33 (18%) of 179 patients receiving TCZ (p = 0.41), regardless of drug formulation (18% for intravenous and 19% for subcutaneous route). Fatal outcomes were observed in 20% of patients in the standard therapy group and in 7% of patients on the TCZ group (p <0.0001). In the TCZ group, mortality did not depend on the TCZ dosage form (7% when the drug was administered intravenously, and 8% of patients subcutaneously). TCZ treatment was associated with a significant reduction in mortality risk (HR: 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).

Perrone et al [90] presented preliminary results of a prospective multicenter study TOCIVID-19 (phase IIa), which included 301 patients; 180 (59.8%) of them were treated with TCZ (8 mg/kg, maximum dose 800 mg). When compared with the estimated mortality rate (null hypothesis) of 20% (after 14 days) and 35% (after 30 days), TCZ treatment resulted in a decrease

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in the incidence of mortality after 30 days (22.4%; p <0.001), but not after 14 days of treatment (18.4%; p = 0.52). The effect of TCZ was higher in patients who did not require mechanical ventilation at baseline.

Rossotti et al [91] summarized the results of a retrospective comparative analysis of the efficacy of TCZ in 84 patients with COVID-19 (the majority, 69.8% with critical disease) compared with the control group (n = 184). TCZ treatment was associated with improved survival (HR: 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), which was primarily associated with an increase in the frequency of adverse drug reactions.

In a study of Canziani et al [92], 64 COVID-19 patients received TCZ and the other 64 patients were in the control group. Within 30 days, the frequency (27% and 38%, respectively) and the risk (HR: 0.61, 95% CI 0.33-1.15) of death did not differ in the compared groups. The treatment with TCZ was associated with a decrease in the need for mechanical ventilation (HR: 0.36, 95% CI 0.16 - 0.83, p = 0.017); there were no signs of increased risk of thrombosis, bleeding, or infections.

De Rossi et al [93] presented an analysis of a cohort study that included 158 patients with COVID-19 pneumonia at an early stage of lung failure. Among them, 90 patients received TCZ along with standard therapy (400 mg IV or 324 mg SC). Mortality rate in the TCZ group was 7.7% (7 of 90 patients), and in the control group, it was 50% (34 of 68 patients). TCZ treatment was associated with a significant reduction in the risk of death (HR: 0.057, 95% CI 0.017-0.0187), did not depend on the drug formulation, and was not associated with infectious complications or other ADRs.

Campochiaro et al [94] assessed the outcome of 65 patients with COVID-19 pneumonia; 32 of these patients received TCZ. After 28 days, clinical improvement was noted in 69% of patients receiving TCZ and in 61% of patients who received standard therapy (p = 0.61); mortality rates were 15% and 33%, respectively (p = 0.15). In the TCZ group, older age correlated with the risk of death, and a high PaO2/FiO2 ratio was associated with clinical improvement. The incidence of infectious complications in the compared groups (13% and 12%, respectively) was similar.

Carvalhoet et al [95] compared the efficacy of TCZ in 28 patients with severe COVID-19 in the ICU and in 24 patients in the control group. Despite the initially more severe condition (the need for GC, mechanical ventilation, a marked decrease in gas exchange) of patients in the TCZ group, there was no increase in mortality (p = 0.3) and in the incidence of infectious complications

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in theTCZ group. In the TCZ group, a more rapid normalization of CRP concentration (p = 0.009), lymphocyte levels (p = 0.02) and lung function was noted.

Mikulska et al. [96] conducted an observational single-center study, which included 196 patients with severe COVID-19 pneumonia. 130 patients received anti-inflammatory therapy, including 29 (22.3%) patients who received TCZ (8 mg/kg, IV or 162 mg, subcutaneously), 45 (34.6%) patients who received methylprednisolone (1 mg/kg for 5 days, intravenously) and 56 patients who received (43.1%) TCZ and methylprednisolone with standard therapy; the remaining patients received the standard therapy. In this study, an early (within 3 days after hospitalization) initiation of treatment with TCZ and/or methylprednisolone was associated with better survival rates: 86.5% and 80.8% after 14 and 30 days respectively vs 64.1% in the standard therapy group. This data showed significant decrease in the risk of treatment failure (HR = 0.48, 95% CI 0.23-0.99, p = 0.049).

In a large observational study, there was no correlation between the treatment with GC (as monotherapy or in combination with azithromycin) and mortality in patients with COVID-19 (n = 2512) [97]. In contrast, in the group of patients receiving TCZ (n = 134), had a tendency for improvement in survival (HR 0.76, 95% CI 0.57-1.00) within 30 days (46%) compared with 56% in the group of patients who did not receive TCZ.

According to Wadud et al. [98] the survival rate of patients with COVID-19 who received TCZ treatment (n = 44) was significantly higher than in the control group (n = 50) (61.36% vs 48.0%, p <0.00001).

Rojas-Marte et al. [99] compared the incidence of deaths in 193 patients with COVID-19, among whom 96 patients received TCZ, and 97 received standard therapy. In general, there were no differences in the mortality rate in the compared groups (52% vs 62%, p = 0.09); however, when comparing patients who did not require mechanical ventilation, TCZ treatment was associated with a significant decrease in mortality, as compared with the control group (6% vs 27%, p = 0.024).

In a prospective study described by Ramino et al [100], 86 COVID-19 patients received TCZ, and 86 patients were 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 manifestations indicating the development of CSS: rapid development of respiratory failure, and at least 2 of 3 laboratory abnormalities (increase in CRP level > 100 mg/L, ferritin> 900 μg/L, D-dimer> 150 μg/L). TCZ (8 mg/kg, IV) was administered in the case of progression of lung impairment over 2 days despite the use of methylprednisolone. As compared to the control

group, the treatment with TCZ was associated with an increased lung recovery rate, more frequent patient discharge from hospital (HR: 1.8, 95% CI 1.2-2.7) (at day 7), 65% decrease in mortality (HR: 0.35, 95% CI 0.19-0.65), and reduced need for mechanical ventilation (HR 0.29, 95% CI 0.14-0.65). The incidence of ADRs was similar, with the exception of increased frequency of pulmonary embolism in the TCZ group (p = 0.0590).

Moreno-Garcia et al. [101] compared the results of TCZ treatment in 77 COVID-19 patients with ARDS vs. control group (n = 94). TCZ treatment was associated with reduced need for transfer to the ICU (10.3% vs 27.6%, p = 0.005), reduced need for mechanical ventilation (0 vs 13.8%, p = 0.001), as well as lower values of the combined parameter: transfer to the ICU and death (OR: 0.03, 95% CI 0.007 - 0.10, p = 0.0001).

Kimming et al. [102] analyzed the outcomes of 111 patients; 48 of them received TCZ. The mortality rate was higher in the TCZ group (39.6% vs 17.4%, p = 0.016). TCZ treatment was associated with a higher risk of secondary bacterial infections (50% vs 28.6%, p = 0.021), fungal infections (8.3% vs 0%, p = 0.78) and mortality rate (39.6% vs 17.7%, p = 0.016). TCZ treatment was an independent risk factor for bacterial infections (OR: 2.82; 95% CI 1.14-7.39, p = 0.0248). In addition, the development of infections positively correlated with the APACHE II indices (OR: 1.079; 95% CI: 1.01-1.16, p = 0.021).

Strohbehn et al [103] conducted a phase II study (COVIDOSE) to evaluate the efficacy of low doses of TCZ (40-200 mg) in patients with COVID-19 who did not require mechanical ventilation. Group A consisted of 8 patients receiving TCZ at a dose of 200 mg and 4 patients receiving 120 mg, and group B received 80 mg (n = 15) and 4 mg (n = 5). Compared with retrospective controls (n = 41), TCZ treatment resulted in a significant decrease in body temperature: 75.0% vs 34.2%, p = 0.001, and CRP level: 86.2% vs 14.3%, p <0.001, within 24-48 hours. There was no correlation between the TCZ dose and changes in these parameters (p = 0.080 and p = 0.10, respectively). Mortality rate within 28 days was 15.6%. A total of 5 (15.5%) patients had clinical or bacteriological signs of infection. Any effect of TCZ on the production of antibodies to SARS-CoV-2 was not observed.

Meta-analysis TCZ studies

Two meta-analyses [104,105] summarized the information from most of the studies mentioned above. In these meta-analyses, the efficacy of TCZ was assessed in patients with COVID-19.

A meta-analysis of Kaye et al [103] included 9 studies with a control group [77, 82, 83, 89, 94, 97-98]; a total of 618 patients received TCZ and 1057 patients were in control groups. This meta-

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analysis showed that the mortality rate was 26.1% in the TCZ groups and 41.5% in the control groups (odds ratio 0.492, 95% CI 0.326-0.713, p <0.001).

In non-controlled studies (n = 803 patients) [59-63, 66-68, 71, 72], mortality rate in patients treated with TCZ was 13.5%.

Another meta-analysis of Boregowda et al [105] was based on the results of 13 retrospective [59-63, 65-67, 73, 77] and 16 prospective [78-85, 88, 89, 94, 96, 99, 101] studies. A total of 2488 patients received standard therapy and 1153 patients received TCZ. This meta-analysis showed that mortality in the TCZ group (22.4%) was significantly lower than in the control group (26.21%) (odds ratio 0.57, 95% CI 0.36-0.92, p = 0.02).

As mentioned earlier, the phase 3 COVACTA (NCT04320615) Trial of Actemra in hospitalized patients with severe COVID-19 associated pneumonia did not meet the primary endpoint of improved clinical status and the key secondary endpoint of reduced patient mortality (129).

Sarilumab and siltuximab

E Gremese et al [106] presented data regarding the use of sarilumab (SAR) in 53 patients with severe COVID-19 pneumonia. 39 patients (66.7%) were treated with SAR (1 infusion) in the Internal Medicine Department, 14 patients (26.4%) in the ICU (92.6% received 2 infusions). Among the patients who were in the Internal Medicine Department, 89.7% showed significant clinical improvement (in 46.7% of patients after 24 hours, in 61.5% - after 3 days), 85.7% of patients did not need supplemental oxygen, 70.6% were discharged from the hospital; 62.4% of patients were transferred from the ICU to the Internal Medicine Department, 35.8% continued to stay in the ICU. The overall mortality rate was 5.7%, including 2.5% (1 patient) in the Internal Medicine Department and 14.4% (2 patients) in the ICU.

In the study of E Della – Torre et al [107], 28 patients with COVID-19 pneumonia received SAR (400 mg, intravenous), and another 28 patients were in the control group. After 28 days in the SAR group, clinical improvement was observed in 61% of patients, the mortality rate was 7%; similar results were obtained in the control group: 64% and 18%, respectively (p> 0.05). In the

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SAR group, clinical improvement correlated with PaO2/FiO2 ratio>100 mm Hg and lung impairment <17% on computed tomography. In patients with lung impairment <17% who received SAR, clinical recovery was faster (on average after 10 days) than in patients who received standard therapy (on average after 24 days) (p = 0.01).

In the study of M Benucci et al [108], lung recovery, estimated by the SpO2/FiO2 ratio, was observed in 7 out of 8 patients with COVID-19 pneumonia who received TCZ treatment. Clinical recovery was associated with an increase in lymphocyte count, reduced IL-6, and CRP levels.

Meanwhile, preliminary results of a multicenter RCT (phase II/III) of SAR, which included 400 COVID-19 patients in severe or critical condition (the need for mechanical ventilation, high-speed nasal flow, and/or hospitalization in the ICU), are disappointing [109]. The phase II interim analysis did not reveal significant differences in the efficacy of therapy with SAR 400 mg IV (n = 145) vs. control group (n = 77) for all analyzed endpoints: mortality rate (23% versus 27%), the need for mechanical ventilation (23% versus 27%), clinical improvement (59% versus 41%), discontinuation of high-speed nasal flow procedures (58% versus 41%), and hospital discharge (53% versus 41%). The only relevant finding was a more pronounced decrease in the concentration of CRP in the SAR group vs. control group (-79% versus -21%).

Preliminary results on the efficacy and safety of SLT have been obtained in 21 patients with COVID-19 complicated by ARDS [110]. In general, the efficacy of therapy can be assessed as satisfactory. All patients showed normalization (within 5–7 days) of CRP levels, 2 out of three patients showed improvement or stabilization of lung function. Nevertheless, 5 patients showed exacerbation of the disease (one patient died), requiring mechanical ventilation.

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5. Future perspectives

Despite the undoubted efficacy of IL-6 inhibitors in patients with severe COVID-19, the role of these drugs and IL-6 in the pathogenesis of CSS should be further investigated [111-113]. In patients with severe COVID-19, the average concentration of IL-6 in the blood serum is significantly lower (in the range from 7 to 627 mg/ml, on average 132.32 ± 278.54 pkg/ml) [26,114-117] than in patients with ARDS caused by other viral infections (578-1618 pg/ml) [118-120]. Viral pneumonia in COVID-19 is thought to be associated with severe local inflammation rather than systemic hyperimmune response associated with ARDS.

The plasma concentration of IL-6 in patients with CSS as a complication of CAR-T-cell therapy reaches 10,000 pg/ml; that is 1000 times higher than in patients with CSS triggered by COVID-19 [121].

An increase in IL-6 concentration up to 50 pg/ml is often observed during active inflammationin patients with rheumatoid diseases in the absence of ARDS and other manifestations of cytokine storm [122-125]. Administration of recombinant human IL-6 to cancer patients at a dose range from 10 μg/kg to 20 μg/ml leads to a pronounced increase in serum IL-6 concentration (>4000 pg/ml), and was not associated with severe lung impairment or multi-organ failure [126]. IL-6 plays an important role in antiviral and antibacterial defense mediatedby the immune system [127]. As a result, treatment with IL-6 inhibitors in patients with rheumatoid arthritis may lead to infectious complications and other ADRs [35,].

In RECOVERY (Randomized Evaluation of COVid-19 thERapY) study, therapy with dexamethasone (6 mg per day for 10 days) was associated with reduced mortality (within 28 days) in patients with COVID-19 (n = 2104) who were on mechanical ventilation (from 40% to 28%; p = 0.0003) or on supplemental oxygen (from 25% to 20%; p = 0.0021), as compared to the control group (n = 4321). In patients who did not receive supplemental oxygen, the superiority of dexamethasone was not demonstrated (p = 0.14) [128]. Thus, the issues of the comparative efficacy of IL-6 and GC, advantages of combination therapy with IL-6 and GC, optimal timing of initiation of treatment with these drugs, and the choice of patients for whom this therapy will be most effective should be further investigated.

Recently, preliminary results of COVACTA clinical trial has been announced. There was no statistical difference between tocilizumab vs placebo arm in severe COVID-19. TCZ didn't meet

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its primary and secondary endpoints: the difference in clinical status (p=0.36), the percentage that died by week four (19.7% vs 19.4%; p=0.94), the difference in ventilator-free days (22 days vs 16.5 days; p=0.320) and at week four rates of infections (38.3% vs 40.6%), and the rates of 'serios infections (21.0% vs 25.9%). However, the median time to discharge or 'ready to discharge' was 20 days in TCZ vs 28 days in placebo (p=0.03), the difference cannot be considred ststistically significant [129]. Early SAR didn't meet key endpoints in COVID-19 trial [109]. Observed data emphasize heterogenecity of cytokine storm immunopathology mechanism in COVID-19. Therefore, GC maybe uniqluy positioned in antiinflammatory control due to inhibiting broader range of cytokines IL-6, IL-1α/β, IL-12, IL-17, IFN-γ, TNF-α (130).

It should be emphasized that the "Treat to Target" (T2T) strategy has been successfully adapted in rheumatology since long ago; T2T mandates early aggressive therapy (within "window of opportunity") with the most effective drugs to achieve remission of the disease [130]. We believe that some provisions of T2T are applicable in COVID-19, regardless of significant differences between IMIRDs (with rheumatoid arthritis as a model), characterized by a relatively slow progression, and COVID-19, with very fast deterioration to potentially lethal CSS, at least hypothetically. T2T strategy can be reasonably implemented in COVID-19 during a "short" period of time in the viremic phase, when cytopathic effects of the virus have already initiated early ("protective", but not always effective) antiviral immune response, which in some patients converts into a hyperimmune phase, progressing towards CSS. Unfortunately, combined use of currently available antivirals and supposedly "dual-acting" drugs (i.e., hydroxychloroquine) in COVID-19 patients do not adequately open "the window of opportunity" to T2T goals in a certain category of patients who, for a number of not yet clear reasons, remain at a high risk of developing CSS. "Repositioning" of Baricitinib (BARI), a targeted synthetic JAK 1/2 inhibitor widely used for RA, can improve this situation. Via inhibition of JAK1 and JAK2, BARI disables the signaling of a wide range of proinflammatory cytokines, including IL-6, GM- CSF, and IFNγ [131].

Moreover, BARI, by binding to AP2-associated protein kinase (AAK1), a pivotal regulator of clathrin-dependent endocytosis, might also inhibit SARS-Cov-2 entry into target cells [132,133]. Preliminary results of an open study indicate the clinical success of early (≤ 6 days) initiated BARI therapy (4 mg per day for 2 weeks) in patients with mild/moderate COVID-19-pneumonia [134]. Some hopes are pinned on another JAK inhibitor, Ruxolitinib a selective JAK1/2 inhibitor, recently approved by the US FDA (US Food and Drug Administration) for treatment of steroid-refractory graft-versus-host disease, often complicated by uncontrolled inflammatory

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damage to major internal organs [135]. There are also reports of Ruxolitinib efficacy in adult patients with secondary HLH [136-138] and COVID-19 pneumonia [139,140]. Major concerns with early use of IL-6 and JAK inhibitors in COVID-19 are related to potential immune suppression during ongoing anti-viral immune response [141], challenging the administration of these agents in the early period of COVID-19 during the viremic phase. However, reported preliminary data suggests that IL-6 itself can maintain the persistence of viruses via different mechanisms, including downregulated expression of perforin and granzyme in natural-killer (NK) cells involved in antiviral immunity [142].

In the broader context of immunomodulatory "personalized therapy" [143-145] there is an ongoing intensive search within the concept of cytokine-based disease taxonomy [146,147] for other adequate therapeutic targets to manage CSS in patients with COVID-19. Apart from IL-6, the relevance of other proinflammatory cytokines inhibition is being extensively explored (or discussed): IL-1β [148,149], TNFα [150], GM-CSF [151], IL-17 [152], IL-18 [153], as well as activation of the complement system [154].

One among newly emerged pharmacotherapy trends is based on IL-1inhibition. IL-1 inhibitors: Anakinra (a recombinant antagonist of the IL-1 receptor) and Canakinumab (mAb to IL-1β), are very effective in a wide range of autoinflammatory diseases [148]. Anakinra was successfully used in sepsis [155], HLH [149, 156], and MAS [157]. Just recently, successful use of Anakinra, as well as IL-6 inhibitors, was reported in patients with severe COVID-19 pneumonia [158-166].

GM-CSF, a proinflammatory cytokine synthesized primarily by myeloid cells and involved in differentiation and proliferation of neutrophils, dendritic cells, macrophages, and endothelial cells [167] is considered as a potential therapeutic target for both RA [168] and possibly COVID-19 [169,170]. GM-CSF signaling is mediated by JAK2 and is potentially blocked by BARI and other JAK inhibitors. A dedicated RCT (BREATH) is planned to evaluate the efficacy and safety of humanized anti-GM-CSF mAbs in patients with severe COVID-19 complicated by ARDS [171].

The complement system, on the one hand, is an important component of the innate immune response against viral infections, and on the other, it plays an essential role in inflammatory damage to organs and tissues [172]. Massive deposits of activated complement components (C3A) in biopsied lung tissue specimens, increased serum concentrations of C5A (anaphylatoxin), deposits of C5b-9 (membrane-attacking complex), as well as C4D and serine

protease associated with mannose-associated lectin (mannose lectin-associated serine protease) in skin and lungs microvasculature were detected in COVID-19 patients. Therefore, provided evidence confirms that activated via alternative and lectin pathways complement system operates as a tasked effector mechanism of systemic micro thrombosis (thrombo-inflammation) in COVID-19 [173]. Preliminary results are indicative efficacy of Eculizumab (humanized mAb, IgG2/4k, blocks the C5A component of the complement and inhibits the production of a membrane-attacking complex) [174] as well as new low-molecular-weight C3A inhibitor of the compstatin family (AMI-101) [175] in patients with COVID-19 complicated by ARDS.

Intravenous immunoglobulin (IVIG) with a wide range of immunomodulatory, antiviral ,and antibacterial effects [176] is also used in COVID-19 patients with severe exacerbations of immuno-mediated diseases and sepsis. A series of studies demonstrated the positive effects of multiple IVIG infusions in severe COVID-19 [177,178].

Therefore, the challenge of CSS in COVID-19 has engaged many areas of scientific and clinical research involved in the exploration of immunopathogenic mechanisms and therapeutic approaches to the management of IMIRDs in an unprecedentedly short time. Hopefully, the extraordinary efforts of scientists and physicians around the world will not only improve the prognosis for COVID-19 patients, facilitate the accumulation of valuable knowledge to control successful epidemics of viral infections that humanity may face in the future, but will also contribute to the improvement of current pharmacotherapy of widespread IMIRDs.

6. Research transparency

This study had no sponsorship. The author is fully responsible for submitting the final version of the manuscript to the press.

7. Declaration of financial and other relationships

The author independently developed the concept of the article and prepared the manuscript. The author did not receive a fee for the article.

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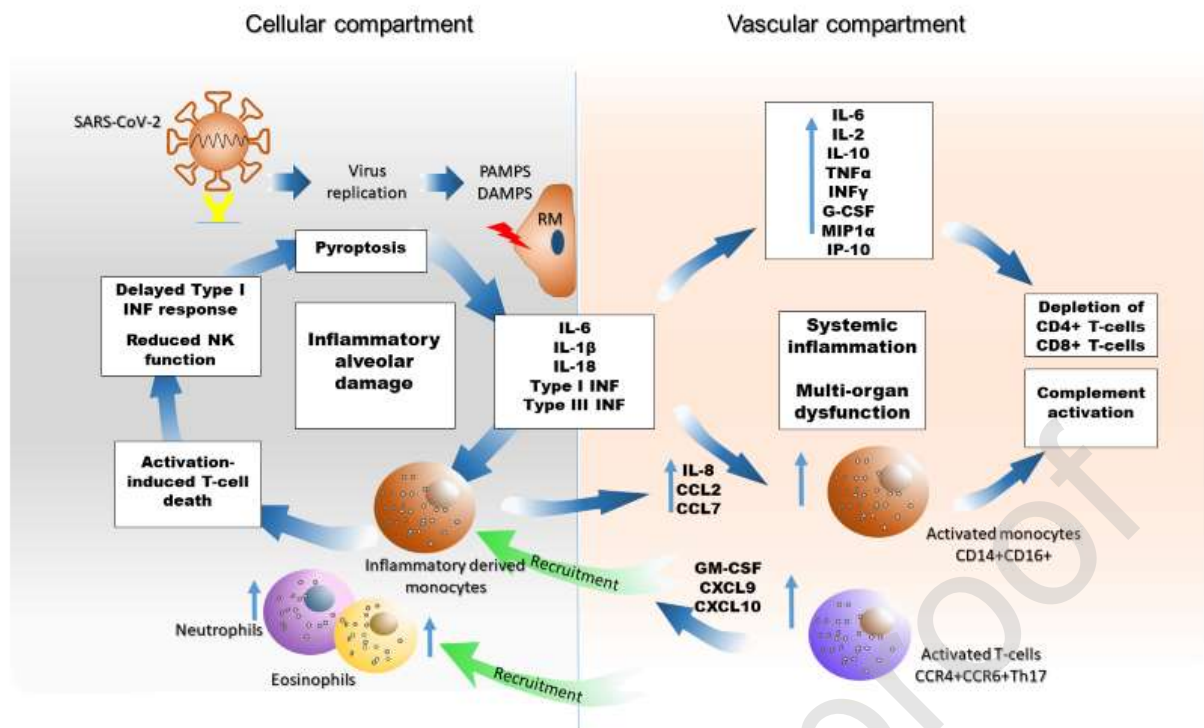
Figure 1. Dysregulation of immune response underlying severe COVID-19 development

RM, Resident macrophages; INF, interferons; NK, natural killers; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor, TNFα, tumor necrosis factor alpha; IP-10, interferon (IFN)γ-induced protein 10; MIP1α, macrophage inflammatory protein; CCL2, CCL7, CXCL9, CXCL10, chemokines.
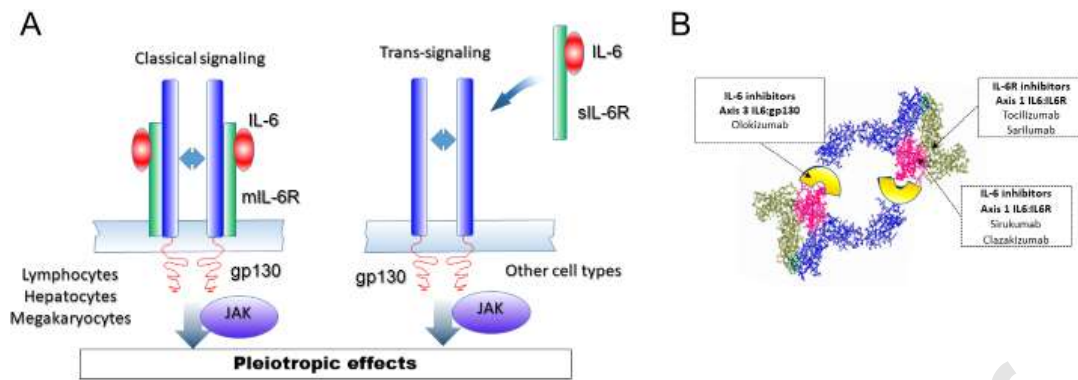
Figure 2. IL-6 receptor complex and IL-6 signaling inhibitors
(A) Classical IL-6 signaling pathway and trans signaling pathway; (B) Binding sites at IL-6 signaling complex for therapeutic IL-6 inhibitors

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