Efficacy of Different Types of Therapy for COVID-19: A Comprehensive Review

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Abstract: A new coronavirus disease (COVID-19) has already affected millions of people in 213 countries. The possibilities of treatment have been reviewed in recent publications but there are many controversial results and conclusions. An analysis of the studies did not reveal a difference in mortality level between people treated with standard therapy, such as antiviral drugs and dexamethasone, and new antiviral drugs/additional immune therapy. However, most studies describe clinical improvement and a decrease in mortality among patients with severe and critical conditions, with the early initiation of additional immune therapy. Possible new targets based on viral life cycles were considered. Unfortunately, the data analysis on the efficacy of different medicine and therapy regimens among patients with COVID-19, showed little success in decreasing the mortality rate in all treatment methods. Some efficacy has been shown with an immunosuppressive therapy in small patient samples, but when a larger number of patients were analyzed the data did not differ significantly from the control groups.

Keywords: coronavirus infection; SARS-CoV-2; COVID-19; antiviral therapy; immune therapy; cytokines; plasma; intravenous immunoglobulin IgG

1. Introduction

The first novel coronavirus cases were officially recorded in Wuhan, Hubei Province, China (PRC) at the end of December 2019 [1,2]. At the end of 2019, the spread of the novel coronavirus caused by the SARS-CoV-2 virus led to the death of patients in 4–22% of cases [3,4], which were associated with severe manifestations of the disease, most often in adults with concomitant pathologies [5–7].

There is currently no etiological treatment for coronavirus infection, and a standard therapy is based on the pathogenesis of the disease. According to the pathogenesis established by Chinese scientists, the process can be divided into three stages [8]. Coronaviruses entering the mucosa of the upper respiratory tract are likely replicated in the cells of the ciliary epithelium [9] and cause rhinitis, glossitis, and a cough with possible systemic intoxication, manifested by fever and arthralgia [10]. When overcoming the upper respiratory tract barriers, the virus enters the lungs, where it binds to the angiotensin converting enzyme 2 (ACE2)
enzyme (ACE) using the receptor-binding domain (RBD) S1 of the subunit of the surface S (spike) protein, which initiates virion endocytosis in the cell [11–13]. From the lungs, the virus enters the systemic circulation known as the viremia phase. During this stage, the virus attacks cells that also express ACE: type 2 pneumocytes in the alveolar epithelium, heart, kidney, gastrointestinal tract cells, macrophages [14–16], as well as the endothelium of arterial and venous vessels, smooth muscle cells in the arteries [17]. The second stage is the acute phase, characterized by organ lesions due to infection. They can be explained by several mechanisms: the direct cytotoxic effect of the virus on cells, immune-mediated complications, vascular complications, and autoimmune side effects [8,18]. The SARS-CoV-2 virus induces a weak interferon response of types I, II and III and a strong activation of the interleukin IL-1β/IL-6 pathway [19]. In the lungs, infection of type II alveolar epithelial cells activates the inflammasome, which induces the production of IL-1β [20]. IL-1β induces the secretion of IL-6 by endothelial cells and vascular smooth muscle cells, which enhance the inflammatory response [21]. In the lungs immune-competent cells infiltrate the tissue and cause an additional alteration due to excessive secretion of proteases and active forms of oxygen [15,22]. The diffuse alteration of alveoli is characterized by the desquamation of alveolar cells, formation of hyaline membranes, development of lung edema and fibrosis [17,23]. It is important to note that the acute phase, characterized by the development of pneumonia, with adequate treatment and normal functioning of the immune system is followed by a stage three recovery. In risk groups (advanced age, the presence of concomitant diseases), the immune system cannot effectively control the course of the diseases. For this reason, serious life-threatening complications such as cytokine storm and massive thrombosis may occur. In such cases, patients end up in a very serious condition and need intensive care [8].

Therefore, existing therapy is aimed at inhibiting viral replication, as the binding to ACE2 and the activity of viral enzymes prevent the vascular and the immune complications from functioning (Figure 1). Despite the wide choice of drugs available, doubts about their efficacy, the most optimal prescription time, and patient selection criteria for certain drugs remain.

![Figure 1](https://example.com/figure1)

**Figure 1.** The targets of drugs used in clinical practice and their influence on pathogenic processes. Abbreviations: EC are endotheliocytes, PC are pneumocytes, NP are neutrophils, and MP are macrophages.
The purpose of this review is to analyze the efficacy of antiviral and immunological treatments of COVID-19.

2. Results and Discussion

2.1. Antiviral Therapies

According to the presented data (Table 1), there is only an insignificant efficacy of hydroxychloroquine sulfate when used in conjunction with azithromycin and a low efficacy as a preventive monotherapy.

Table 1. The results of the studies on the efficacy of antiviral drugs for COVID-19 treatment.

| N  | Authors and Year of Publication | The Agent Studied | Mode of Drug Administration | Number of Patients/Control Group | Observation Time, Days (Median) | Comparison of Efficiency with Control Group (%) | Conclusions |
|----|--------------------------------|-------------------|-----------------------------|---------------------------------|---------------------------------|-----------------------------------------------|-------------|
| 1  | Cao B. et al., 2020 [24]       | lopinavir/ritonavir| 400/100 mg twice a day 14 days | 99/control (n = 100)            | 28                             | Mortality 19.2 vs. 25.0                         | No difference |
| 2  | Li Y et al., 2020 [25]         | lopinavir/ritonavir| 200/50 mg 2 times/day 7–14 days and 200 mg 3 t/day 7–14 days | 34 versus 35 and control (n = 17) | 21                             | Efficacy: 85.3 vs. 91.4 vs 76.5                |
| 3  | Gautret Ph. et al., 2020 [26]  | Hydroxychloroquine sulfate | 600 mg/ day 10 days | 20/control (n = 16)           | 14                             | Efficacy: 57.1 vs. 12.5                        |
| 4  | Gautret P, et al., 2020 [27]   | hydroxychloroquine sulfate + azithromycin | 600 mg/ day 10 days + 500 mg on 1-st day, further 250 mg 2nd–5th day | 80/no                          | ≥6                              | Efficacy: 93.0                                |
| 5  | Geleris J. et al., 2020 [28]   | hydroxychloroquine sulfate | 600 mg on 1-st day, further 400 mg/day | 811/control (n = 565)       | 22.5                            | Efficacy: 45.8 (no data)                       |
| 6  | Grein J. et al., 2020 [29]     | remdesivir           | 200 mg on 1-st day, further 100 mg 2nd–10th day | 53/no                          | 19                              | Efficacy: 47.0 (no data)                       |
| 7  | WangY. et al., 2020 [30]       | remdesivir           | 200 mg on 1-st day, further 100 mg 2nd–10th day | 158/placebo control (n = 79) | 28                              | Efficacy: 65.0 vs. 58.0                        |
| 8  | Beige JH. et al., 2020 [31]    | remdesivir           | 200 mg/day for 10 days | 538/placebo control 521       | 15                              | Efficacy: 62.9 vs. 52.7                        |
| 9  | Goldman JD.et al, 2020 [32]    | remdesivir           | 200 mg/day for 5 and 10 days | 200 (5 days)/197 (10 days)     | 14                              | Efficacy: 64.0 vs. 54.0 Mortality 8.0 vs 11.0 |
| 10 | Boulware D.R. et al., 2020 [33]| hydroxychloroquine sulfate (prophylactically) | 800 mg a single dose, further 600 mg after 6 and 8 h, further 600 mg for 4 days | 414 patients with asymptomatic course/407 (placebo) | 14                              | Got sick 11.8 vs. 14.3                        |
| 11 | Freedberg ED et al., 2020 [34]| famotidine           | 20 mg, 40 mg, 10 mg | 84/control 1536              | 5                               | Mortality 10.0 vs. 22.0                       |
| 12 | Horby P. at al, 2020 [35]     | hydroxychloroquine sulfate | 800 mg a single dose, further 400 mg after 12 h and 6 days | 1561/3155 (control) | n                               | Mortality 27.0 vs. 25.0                       |
Table 1. Cont.

| N  | Authors and Year of Publication          | The Agent Studied                                                                 | Mode of Drug Administration | Number of Patients/Control Group | Observation Time, Days (Median) | Comparison of Efficiency with Control Group (%) | Conclusions               |
|----|----------------------------------------|-----------------------------------------------------------------------------------|----------------------------|----------------------------------|---------------------------------|-----------------------------------------------|--------------------------|
| 13 | Mather J et al., 2020 [36]             | famotidine + hydroxychloroquine sulfate 
  
  \(n = 36\) 

  famotidine + azithromycin 
  
  \(n = 36\) 

  famotidine + corticosteroids 
  
  \(n = 48\) | 20 mg, 40 mg 7 days | 83/689 (control group) | 36 | Mortality 21.6 vs. 39.7 |

A study of the efficacy of remdesivir in conjunction with COVID-19 was carried out in 53 patients with a confirmed SARS-CoV-2 virus carrier based on PCR and respiratory failure (an oxygen saturation of \(\leq 94\%\)/the need for oxygen support) [29]. In 68% of cases, there was an improvement in the oxygen support class, including 17 out of 30 patients who were on mechanical ventilation, and later extubated. The mortality level in the patient group who received invasive ventilation was 18% (6 out of 34) and 5% (1 out of 19) among those who did not need invasive ventilation. Furthermore, in a larger number of patients with COVID-19, another randomized trial was conducted and its findings indicated the results for the treatment of 538 patients and proved the effectiveness of the drug within 15 days of observation, compared with the control group who received a placebo \((n = 521)\). However, the number of deaths in the groups did not significantly differ (7.1% versus 11.9%) [25].

One of the most significant studies with an analysis of a large number of clinical cases was devoted to the efficacy of dexamethasone in COVID-19 treatment [37]. A decrease of 10% in mortality rate was observed among patients with mechanical ventilation (29.3% vs. 41.4%). The analysis of the total mortality rate among COVID-19 patients with dexamethasone was not as significant (22.5% vs. 25.7%).

2.2. Immune Therapy

There are several directions that can be taken for the development of immune therapy for coronavirus infection [38]:

- Monoclonal antibodies against cytokines and their receptors;
- Kinase inhibitors;
- Polyclonal antibodies by plasma therapy;
- Intravenous immunoglobulin IgG (IVIG);
- Polypeptide hormone for maturation of T cells.

2.2.1. Monoclonal Antibodies against Cytokines and Their Receptors

According to the pathogenesis of hyperinflammation in COVID-19, the main participants are IL-1\(\beta\) and IL-6; therefore, the focus of clinical research was to study drugs which can block the signaling pathways of these molecules [19].

The results of 15 different studies using drugs to block the signaling pathways of IL-1\(\beta\) and IL-6 in patients with COVID-19 of varying levels of severity, are presented in Table 2. We can see that employing the described drugs had a beneficial effect in reducing the severity of the disease; however, in most cases, the summary indicators (survival/mortality) were similar to the control group.
Table 2. The results of the studies on the efficacy of the drugs blocking the IL-1β and IL-6 signaling pathways for COVID-19 treatment.

| № | Authors, Year | The Type of the Study | The Drug | The Treatment Characteristics of Patients | Comparison Group | Conclusions |
|---|---------------|-----------------------|----------|-------------------------------------------|-----------------|-------------|
| 1 | Cavalli G et al. [39] | Retrospective cohort study | Anakinra (block IL-1 beta R) | Patients (aged ≥ 18 years) with COVID-19, ARDS, and hyperinflammation (n = 29) | Standard treatment + Anakinra dose 5 mg/kg twice a day 100 mg subcutaneously 21 days | COVID-19, ARDS, and hyperinflammation Standard treatment | Decreased mortality |
| 2 | Pontali E. et al. [40] | Uncontrolled cohort study | | 5 patients with severe/mild COVID-19 100 mg IV every 8 h n = 5 | - | Faster de-escalation of the intensity of care |
| 3 | Ucciferri C et al. [41] | Retrospective cohort study | Canakinumab (block IL-1β) | n = 10 | - | Faster de-escalation of the intensity of care |
| 4 | Xu X et al. [42] | Retrospective cohort study | Tocilizumab (block IL-6) | 4–8 mg/kg, recommended dose–400–800 mg singly 21 days | - | Faster de-escalation of the intensity of care |
| 5 | Malekzadeha R et al. [43] | Multicenter, prospective, open-label, uncontrolled | | Adult patients with severe and critical COVID-19 n = 126 | 324 mg (<100 kg bodyweight) or 486 mg (≥100 kg bodyweight), 40 days | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states n = 161 | No difference |
| 6 | Stone JH et al. [44] | A randomized, double-blind, placebo-controlled trial | | Severe COVID-19 n = 48 | 4–8 mg/kg, recommended dose–400–800 mg singly 14 and 28 days | Severe COVID-19 n = 81 | Standard treatment |
| 7 | Alattar R et al. [45] | Retrospective cohort study | | 4–8 mg/kg, recommended dose–400–800 mg singly 14 and 28 days | - | No difference |
| 8 | Tsai A et al. [46] | A single-center propensity-score matched cohort study | | Severe COVID-19 n = 66 | 8 mg/kg, recommended dose–400–800 mg singly | Severe COVID-19 n = 81 | No difference |
| 9 | Klopfenstein T et al. [47] | a retrospective case-control study | | Severe COVID-19 n = 20 | tocilizumab (1 or 2 doses) severe COVID-19 n = 100 | Severe COVID-19 n = 25 | Standard treatment |
| 10 | Toniati P et al. [48] | | | 8 mg/kg by two consecutive intravenous infusions 12 h apart | - | Decreased mortality, Faster de-escalation of the intensity of care |
Table 2. Cont.

| №  | Authors, Year | The Type of the Study | The Drug | The Treatment Characteristics of Patients | Conclusions |
|----|---------------|-----------------------|----------|--------------------------------------------|-------------|
| 11 | Guaraldi G et al. [49] | Retrospective, observational cohort study | n = 179 | intravenously at 8 mg/kg bodyweight (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (ie, 324 mg in total) severe COVID-19 | Adults (≥ 18 years) with severe COVID-19 n = 365 Standard treatment | Decreased mortality |
| 12 | Potere N. et al. [50] | Retrospective case–control study | n = 40 | 324 mg, given as two concomitant subcutaneous injections severe to critical COVID-19 | Severe COVID-19 n = 40 Standard treatment (SOC) | Faster de-escalation of the intensity of care |
| 13 | Rojas-Marte G. et al. [51] | Retrospective, case–control, Single-center study | n = 96 | 4–8 mg/kg, recommended dose 400–800 mg singly 15 and 17 days | Severe to critical COVID-19 n = 97 Standard treatment | Decreased mortality |
| 14 | Colaneri M et al. [52] | Prospective study | n = 21 | 8 mg/kg, recommended dose 400–800 mg singly 7 days | n = 91 Standard treatment | No difference |
| 15 | Tarrytown NY. et al. [53] | Randomized Phase 2 | Sarilumab (block IL-6 R) | Critical, severe COVID-19 \( n = 281 \) 136 (200 mg)/145 (400 mg) | Critical, severe COVID-19 \( n = 77 \) placebo | No difference |

It can be assumed that using cytokine inhibitors is the most appropriate way to treat patients with severe disease and hyperinflammation, where extensive organ damage is not evident and mechanical ventilation support is not needed. Other researchers have come to similar conclusions. Tocilizumab has been described as reducing fever and systemic inflammation within 5–7 days, was associated with improved oxygenation rates within 48–72 h, and also delayed the risk of intubation or mortality [54]. Analysis of clinical trials (RCT-TCZ-COVID-19, CORIMU/NO-19-TOCI-1, BACC Bay Tocilizumab, and STOP-COVID-19) showed that mortality can be reduced by early medication of tocilizumab [55].

2.2.2. The Kinase Inhibitors

Janus kinase inhibitors (JAK) downregulate the phosphorylation of the signal transducer and transcriptional activator (STAT) of several inflammatory proteins. Blocking the JAK inhibits the activation of the immune system and the development of inflammation (for example, the cellular response to proinflammatory cytokines such as interleukin IL-6) [56,57].

Baricitinib, a Janus kinase (JAK) inhibitor of JAK1 and JAK2 kinases, and Bruton’s tyrosine kinase (BTK), a B-cell antigen receptor signaling molecule, are currently being investigated in clinical trials. The data of the studies \( n = 4 \) are shown in Table 3.

According to the analysis of these studies, the use of Janus kinase inhibitors (JAK) was associated with a clinical improvement; however, a reduction in mortality was not achieved. It should be noted that most results were obtained from small numbers of patients with differing degrees of severity which means that, for more accurate results, additional double-controlled studies with stricter inclusion criteria, a larger number of patients, and the presence of comparison groups were needed.
Table 3. The results of the studies on efficacy of Janus kinase inhibitors for COVID-19 treatment.

| №  | Authors, Year | The Type of the Study | The Drug | The Treatment Characteristics of Patients | Conclusions |
|----|---------------|-----------------------|----------|------------------------------------------|-------------|
| 1  | Cantini F et al. [58] | Pilot study with open-label design, with no randomization and a low number of treated patients' | Baricitinib (block JAK-k) | Moderate COVID-19 4 mg/day 14 days n = 24 | Faster de-escalation of the intensity of care |
| 2  | Kalil AC et al. [59] | Multicenter. A randomized, double-blind ACTT-2 trial | Multicenter | Moderate to severe COVID-19 4 mg daily (for up to 14 days or until hospital discharge), n = 515 | Decreased mortality |
| 3  | Cao Y et al. [60] | Small, single-blind, randomized, controlled Phase 2 trial | Ruxolitinib (block JAK-k) | Severe COVID-19 n = 20 5 mg orally twice daily | No statistical difference was observed. |
| 4  | Roschewski M et al. [61] | Retrospective case series | Acalabrutinib (Bruton’s Tyrosine Kinase Inhibitors) | Severe COVID-19 n = 19 - | Faster de-escalation of the intensity of care |

2.2.3. Intravenous Immunoglobulin IgG (IVIG)

According to some studies, IVIG (intravenous immunoglobulin) [62,63] also achieves some efficacy in the treatment of COVID-19. Some information about clinical studies with the use of IVIG are shown in Table 4.

Table 4. The results of the studies on efficacy of IVIG for COVID-19 treatment.

| №  | Authors, Year | The Type of the Study | Treatment Patient Characteristics | Conclusions |
|----|---------------|-----------------------|--------------------------------|-------------|
| 1  | Shao Z et al. [64] | Multicenter retrospective cohort study | Critical COVID-19 n = 174 human Immunoglobulin (pH4) for intravenous injection 28 and 60 days | No difference |
| 2  | Zhou Z-G et al. [63] | Short-term moderate-dose corticosteroid (160 mg/d) plus immunoglobulin (20 g/d) | Critical COVID-19 n = 151 | Faster de-escalation of the intensity of care |
| 3  | Xie Y et al. [62] | Severe or critical illness due to COVID-19 n = 58 | - | Faster de-escalation of the intensity of care |

The obtained data are insufficient for making accurate conclusions; however, it can be noted that the use of IVIG during early stages of the disease is associated with an improvement in the clinical parameters of patients and the prognosis of the disease.
2.2.4. Convalescent Plasma Transfusion

Plasma transfusion can eradicate pathogens from the circulation and neutralize ferritin and cytokines [65,66]. Convalescent plasma generated a lot of enthusiasm during early days of the COVID-19 pandemic due to its plausible mechanism of action and its easy availability from donors [67]. Information about clinical research, which was carried out by studying the efficacy of plasma convalescents with the new coronavirus infection, is provided in Table 5.

Table 5. The results of the studies on efficacy of the use of convalescent plasma for COVID-19 treatment.

| №   | Authors, Year          | The Type of the Study                                         | Treatment Patient Characteristics | Conclusions                                      |
|-----|------------------------|--------------------------------------------------------------|-----------------------------------|-------------------------------------------------|
| 1   | Simonovich VA et al.   | Double-blind, placebo-controlled, multicenter trial         | Severe COVID-19 n = 228           | No difference                                   |
|     | [68]                   |                                                              | Early administration of convalescent plasma (median titer of 1:3200 of total SARS-CoV-2 antibodies) |                                                  |
|     |                        |                                                              | Severe COVID-19 n = 105 placebo   |                                                  |
| 2   | Libster R et al. [69]  | A randomized, double-blind, placebo-controlled trial         | Mildly ill infected older adults n = 80 | No statistical difference reduced the progression of COVID-19 |
|     |                        |                                                              | Early administration of high-titer convalescent plasma 250 mL (IgG titer greater than 1:1000 against SARS-CoV-2 spike) |                                                  |
|     |                        |                                                              | Mildly ill infected older adults n = 80 placebo |                                                  |
| 3   | Salazar E et al. [70]  | Prospective, ongoing study                                   | Severe and/or life-threatening COVID-19 n = 136 | Decreased mortality                             |
|     |                        |                                                              | 600 mL plasma was collected from each donor 7 and 14 days |                                                  |
| 4   | Khamis F et al. [71]   | Single-center, case series study                             | Early therapeutic plasma exchange (TPE), 14, 28 days | Decreased mortality                             |
| 5   | Li L et al. [72]       | Open-label, multicenter, randomized clinical trial           | Severe or life-threatening COVID-19 n = 52 | No difference                                   |
|     |                        |                                                              | specific IgG titer ≥ 1:640; 200 mL of plasma 28 days |                                                  |
|     |                        |                                                              | Severe or life-threatening COVID-19 n = 51 |                                                  |
| 6   | Gharbharan A et al. [73]| A randomized trial                                           | n = 43 ≥ 1:80; 300 mL 15 days | No statistical difference Mortality 14.0 vs. 26.0 |
|     |                        |                                                              | n = 43 |                                                  |
2.2.5. Polypeptide Hormone for Maturation of T Cells

One of the most underexplored fields of research is immunomodulation using thymosin, a polypeptide hormone used for T-cell maturation. Only two clinical trials (ChiCTR-2000029541 and ChiCTR2000029806) used thymosin in combination with a standard therapy [77].

At this moment in time, it is difficult to draw conclusions on the efficacy of the immune therapy of COVID-19. However, most studies describe a clinical improvement and decrease in mortality among patients in a severe and critical condition with the early initiation of additional immune therapy. These findings are supported by the study by Alessia Alunno et al., according to which none of the many immunomodulators had an impact on the mortality of patients; however, there is currently no final decision regarding the use of tocilizumab [78].

It is necessary to carry out a comparative analysis on the efficacy of each type of immune therapy in order to determine the effectiveness predictive factors for certain categories of patients, depending on the severity of the disease, age, concomitant diseases, and the time since the onset of symptoms.

3. Possible Therapy Targets for COVID Treatment

The present therapy has some advantages in its metabolic characteristics, dosages used, and potential efficacy, but “broad-spectrum” medicaments and their side effects should not be underestimated. Therefore, the research on new therapeutic targets and drugs continues to be conducted. The therapies that act on the coronavirus can be divided into several categories based on the specific pathways [79]:

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Table 5. Cont.

| №  | Authors, Year      | The Type of the Study                                                                 | Treatment                                 | Patient Characteristics                  | Conclusions                        |
|----|--------------------|--------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------|-----------------------------------|
| 7  | Agarwal A at al [74]| Open label, parallel arm, phase II, multicentre, randomised controlled trial.       | Moderate COIVD-19                         | $n = 235$                               | No statistical difference         |
|    |                    |                                                                                      | 2 doses of 200 mL CP                      |                                          | Mortality: 14.5 vs. 13.5         |
| 8  | Joyner MJ et al. [75]| Open-label, Expanded Access Program (EAP) for the treatment of COVID-19 patients with human convalescent plasma. | Severe critical COVID-19                  | $n = 35$                               | Decreased mortality              |
|    |                    |                                                                                      | 150–200 mL                               |                                          |                                   |
|    |                    |                                                                                      | 30 days                                  |                                          |                                   |
| 9  | Liu STH et al. [76] | Retrospective, propensity score-matched case-control study                            | Severe or life-threatening COVID-19       | $n = 39$                               | No difference                     |
|    |                    |                                                                                      | 2 units of CP; 1:320                      |                                          |                                   |
|    |                    |                                                                                      | 14 days                                  |                                          |                                   |

The greatest efficacy of the therapy is observed with the early use of plasma (up to 72 h) among patients with a severe level of the disease. A failure response of plasma therapy was noted in a review by Pathak et al. [67].

Perhaps the conflicting results can be explained by the lack of standards and methods for the screening of donor plasma, in search of the presence of binding and neutralizing antibodies to SARS-CoV-2, which could lead to use of plasma with a low level of antibodies [75].
- Enzymes or functional proteins for RNA synthesis and replication, for example: Nsp3 (Nsp3b, e Papain-like proteinase (PLpro)), Nsp7*Nsp8 complex, Nsp9eNsp10, Nsp14eNsp16, Nsp5 (3CLpro), Nsp12 (RdRp), Nsp13 (Helicase);
- Structural proteins for binding to human cell receptors, for example: Spike protein, E-channel, C-terminal RNA binding domain (CRBD), N-terminal RNA binding domain (NRBD);
- Virulence factors damaging the host’s innate immunity, for example: Nsp1, Nsp3c, ORF7a;
- The host’s specific receptors or enzymes, for example: TMPRSSS2, ACE2.

Wu C. et al. [80] conducted a virtual screening of ligands based on 21 targets (including two human targets) and selected molecules capable of inhibiting them. Gordon et al. [81] identified two classes of molecules and experimentally demonstrated their antiviral efficacy: inhibitors of protein biogenesis (zotifine, ternatin-4, and PS3061) and ligands of sigma-1 and sigma-2 receptors (haloperidol, PB28, PD-144418 and hydroxychloroquine, which is undergoing clinical trials). The authors noted the importance of the discovery of antiviral activity in sigma-1 and sigma-2 opioid receptor subtype inhibitors. It is possible that these molecules also contribute to the penetration of the virus into the cells, which may explain some neurological symptoms, in particular anosmia, because the olfactory bulb is rich in these proteins. Possible targets and their role in the life cycle of the virus are shown in the Figure 2.

![Figure 2. Possible therapeutic targets and their role in the life cycle of the SARS-CoV-2.](image-url)

According to these studies, the most promising drugs might be anti-bacterial (Chloramphenicol, Cefamandole, Tigecycline, Lymecycline, Demeclocycline, Doxycycline, Oxytetracycline, Novobiocin, Gallstonedissolving, Drug Chenodeoxycholic Acid, Cefsulodine, Rolitetracyclin, Sulfasalazine, Azlocillin, Penicillin, Pivampicillin, Hetacillin, Cefopera-
zone, Clindamycin, Cefmenoxime, Piperacillin, Cefpiramide, Streptomycin, Lymeceycline, Tetracycline); anti-viral (Ribavirin, Saquinavir, Valganciclovir, Thymidine), anti-tumor (Idarubicin, Zotatifin, Ternatin-4, Ps3061); and anti-hypertensive (Nicardipine, Rescinnamine, Losartan, Conivaptan, Telmisartan, Iloprost, Prazosin). More detailed information is presented in Table 6.

Table 6. Possible therapeutic targets and drugs for COVID-19 treatment.

| The Group of Therapeutic Target | The Target | The Inhibiting Molecule |
|---------------------------------|------------|------------------------|
| Blocking replication            | Papain-like proteinase (PL.pro) | anti-virus drugs (ribavirin, valganciclovir, thymidine) |
|                                 | 3C-like main protease (3CLpro/Nsp5) | anti-bacterial drugs (chloramphenicol, cefamandole, tigecycline) |
|                                 | RNA-dependent RNA polymerase (RdRp) | muscle relaxant drug (chlorphenesin carbamate) |
|                                 | Helicase | anti-tussive drug (levodropropazine) |
| Restoring host’s innate immunity | Nsp1, Nsp3c, ORF7a | anti-bacterial drugs (lymecycline, demeclocycline, doxycycline, oxytetracycline) |
|                                 | Spike protein | anti-hypertensive drugs (nicardipine, telmisartan, conivaptan) |
|                                 | Interface between Spike and ACE2 | anti-fungal drug itraconazole |
|                                 | ACE2 protein | anti-HIV1 drug saquinavir |
|                                 | TMPRSS2 | anti-coagulant drug dabigatran |
|                                 | Ligands of the sigma-1,2 receptors | diuretic drug canrenoic acid |
|                                 | Eukaryotic Translation Initiation Factor 4H (eIF4H) | anti-bacterial drugs (piperacillin, cefpiramide, streptomycin, lymeceycline, tetracycline) |
|                                 | Elongation factor-1A (eEF1A) | antihypertensive drugs (rescinnamine, iloprost, prazosin) |
|                                 | Sec61 translocon | antifungal drugs (posaconazole, itraconazole) |
|                                 | Ligands of the sigma-1,2 receptors | anti-bacterial drug (sulfasalazine, azlocillin, penicillin, cefsulodin) |
|                                 | Eukaryotic Translation Initiation Factor 4H (eIF4H) | anti-coagulant drug dabigatran etexilate |
|                                 | Elongation factor-1A (eEF1A) | Hesperidin |
|                                 | Sec61 translocon | antidiabetes drug troglitazone |
|                                 | Ligands of the sigma-1,2 receptors | antihypertensive drug losartan |
|                                 | Eukaryotic Translation Initiation Factor 4H (eIF4H) | analgesia drug ergotamine |
|                                 | Elongation factor-1A (eEF1A) | anti-bacterial drug cefmenoxime |
|                                 | Sec61 translocon | hepaprotective drug silybin phylaembrilin |
|                                 | Ligands of the sigma-1,2 receptors | anti-bacterial drugs (pivampicillin, hetacillin, cefoperazone, clindamycin) |
|                                 | Eukaryotic Translation Initiation Factor 4H (eIF4H) | Haloperidol, PB28, PD-144418 and hydroxychloroquine |
|                                 | Elongation factor-1A (eEF1A) | Zotatifin |
|                                 | Sec61 translocon | Ternatin-4 |
|                                 | Ligands of the sigma-1,2 receptors | PS3061 |

Additionally, the scientists revealed some natural compounds (catechin compounds with an antioxidant effect and xanthones with an insecticide effect) that can block the viral life cycle in different phases. Some of these are presented in Table 7.
Table 7. Some of the natural compounds considered to have an inhibiting effect on the SARS-CoV-2 life cycle.

| The Plant                  | Scutellaria Baicalensis | Cassine Xylocarpa | Swertia Genus | Citrus Aurantium | Phyllanthus Emblica |
|----------------------------|-------------------------|-------------------|---------------|------------------|---------------------|
| Molecules inhibiting Sars-Cov-2 | Baicalin                | Chrysin-7-O-b-glucuronide | Deacetylcentapicrin | Triptexanthoside D | Neohesperidin        |
|                            | Wogonoside              | Wogonoside        | 1,7-dihydroxy-3-methoxynanthone | Kouitchenside I, D | Hesperidin          |
|                            | Cosmosiin               | Betulonal          | Betulonal Etxilate | Triptexanthoside D | Phyllaembolinol     |
|                            |                         | etxilate          | betulonal      |                  | Phyllaemblicin B, G7 |

4. Conclusions

Unfortunately, the data analysis on the efficacy of different medicines and therapy regimens among patients with COVID-19 showed little success in decreasing the mortality rate through all methods. Some efficacy was shown with immunosuppressive therapy in a small number of patients, but when a larger number of patients was analyzed, the data did not differ significantly from the control groups. Furthermore, initial hopeful results concerning plasma application were ineffective in larger studies. This analysis led us to postulate that there is no evidence for the effective treatment of COVID-19 patients. Despite the presence of a great number of agents and studies conducted, no effective treatment methods were revealed.

Studies on virtual ligand screening and affinity-purification mass spectrometry revealed a wide spectrum of anti-SARS-COV2 molecules, mostly human proteins (opioid like receptors, factors of replication and translation) involved in the virus life cycle, and the molecules that inhibit them.

The most important aspect is the analysis of data on the use of various types of COVID-19 therapy in patients with a severe, critical course of the disease, especially in older age groups.

The analysis showed that, to date, there is no effective antiviral agent for the treatment of COVID-19. According to the previously obtained data, it was demonstrated that the administration of hydroxychloroquine for the treatment and prevention of coronavirus infection is not effective. On the other hand, the use of remdesevir in some patients, including those who were on invasive ventilation, showed an improvement in the course of the disease without a significant effect on mortality.

It was shown that early use of immunosuppressive agents (e.g., tocilizumab, JAK kinase inhibitors, IVIG) may have affected the severity of clinical manifestations, but did not impact mortality.

The first inspiring data on the transfusion of plasma convalescents to patients with COVID-19 were not confirmed. However, subsequent studies of this method with the formation of common standards may improve these results.

The data which demonstrated potential therapeutic targets (mainly from antiviral, antibacterial, and antihypertensive drugs, as well as human proteins involved in the virus life cycle and the molecules that inhibit them) are encouraging, but at the present moment, they are of scientific rather than practical interest.

Thus, according to the results of this analysis, none of the considered methods of COVID-19 therapy showed a significantly positive effect on mortality or a significant effectiveness in comparison with other methods, indicating the need for further research.

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