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Abstract

Background: The rapid spreading of SARS-CoV-2 virus, higher incidence and mortality over population and also insufficient knowledge about the etiology of this disease and methods of its elimination is a problem of modern virology. Series measures are performed to implement an accurate form of therapies for COVID – 19 patients and convalescents. Methods: The purpose of this article is to conduct a systematic review of the latest surveys about effective treatment methods of SARS-CoV-2 infected patients. In order to do this, 46 scientific records from 2019 - 2021 published in the PubMed scientific database were included. Results: The most known, efficient methods of COVID-19 therapy included therapy of tocilizumab, remdesivir and amantadine, which were used separately. Various studies have shown different effects of the drugs mentioned. Some evidence suggests that these treatments contribute to faster recovery, milder course, and lower hospitalization rates in COVID-19 patients. Conclusion: In our review promising therapies and medicaments, which can be used in COVID-19 practice were described. However, none of presented therapies has turned out in 100% efficient in the treatment of COVID-19. The profilled recommendation should be further combined to refine and formulate new effective treatments for SARS-CoV-2.

Key words: Tocilizumab, remdesivir, COVID-19, Coronavirus, rehabilitation, amantadine

Introduction

In November 2019, the several patients in Wuhan (China), were diagnosed on the severe acute respiratory syndrome caused by the SARS-CoV-2 virus. By March 11, 2020, it had spread to different countries and the disease caused by this virus was named COVID-19. In so far, there are no specific and effective methods of treatment of the patients infected by the SARS-CoV-2 virus (1,2). The genome analysis of virus showed the sequence, which is in 75% -80% similar to the SARS-CoV-1 sequence. Therefore, the potential methods of treatment are based on previous experience with comparable virus like SARS-CoV-1, HIV and other viral infections (3).

Several drugs, such as hydroxychloroquine, ribavirin, lopinavir / ritonavir (LPV / r), remdesivir, and oselamivir, have now been proposed as an effective treatment for SARSCoV-2. Lopinavir is an antiretroviral protease inhibitor used in combination with ritonavir, which blocks metabolism of lopinavir in the treatment of patients with acquired immune deficiency syndrome (AIDS) (4).

The virus can be transmitted by air, usually through coughing and sneezing. The incubation period for the disease is usually 2 to 14 days, with an average duration of 5 days. A person can become infected 24 to 48 hours before symptoms appear. COVID-19 can take a variety of courses: asymptomatic, light and severe. This is mainly due to the activity of the immune system and the speed of sending an immune response that can be blocked by age and the development of another disease (2).

The SARS-CoV-2 virus is most common in adult male patients aged 34 to 59. The most common symptoms are: fever, dry cough, shortness of breath, chest pain, fatigue, muscle aches, loss of smell and taste. Rare symptoms include headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting (5,6).
The purpose of this article was to conduct a review of the latest research concerning the most effective forms of therapies for COVID-19 patients and convalescents.

**Material and Methods**

A systematic review of the literature considered as a method of integrating scientific evidence has been performed. Data eligible for review use a public protocol for data identification, selection and analysis. Its goal is to minimize bias and seek accurate and reliable scientific evidence.

Using the PubMed database, a literature review investigating the effect of therapy on COVID-19 treatment was performed. Based on the available literature, the work has been divided into subchapters, taking into account the therapies with tocilizumab, remdesivir, amantadine (Table 1).

The results were obtained using the following keywords: Tocilizumab, COVID-19, amantadine, Rehabilitation.

**Table 1. Stages of literature search**

<table>
<thead>
<tr>
<th>Search stages</th>
<th>Search phrases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tocilizumab, COVID-19, Rehabilitation, amantadine, remdesivir</td>
</tr>
<tr>
<td>2</td>
<td>Publications in English</td>
</tr>
<tr>
<td>3</td>
<td>Publication issued 2019-2021</td>
</tr>
<tr>
<td>4</td>
<td>Available abstract</td>
</tr>
</tbody>
</table>

Selected criteria were taken into account: age of the examined patients, duration of treatment, stage of the disease, possible undesirable symptoms. The publications with literature review and short communications were not taken into account. Own analysis and articles with similar content were adopted as the final criterion (Table 2).

**Table 2. Inclusion and exclusion criteria applicable for the analysis**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. the age of the respondents,</td>
<td>1. literature reviews,</td>
</tr>
<tr>
<td>2. the duration of the treatment,</td>
<td>2. short summaries</td>
</tr>
<tr>
<td>3. stage of the disease,</td>
<td>3. Exclusion of articles with a similar content</td>
</tr>
<tr>
<td>4. possible undesirable symptoms.</td>
<td></td>
</tr>
</tbody>
</table>

**Results and analysis**

46 articles based on COVID-19 treatments during and after infection have been considered and analyzed based on the inclusion and exclusion criteria, the scientific value, credibility and knowledge contained therein (Figure 1).

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**Figure 1. PRISMA 2009 flow diagram**
Effective forms of therapy in patients with COVID-19

Initially, articles on surveys examining the new tocilizumab (TCZ) therapy in several hospitals were analyzed. The study was conducted on patients with a confirmed diagnosis of COVID-19 who were in critical condition (Table 3).

Table 3. Tocilizumab – The results of the analysis of individual articles

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Aim</th>
<th>Material and Methods</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sohaib Roomi</td>
<td>The aim of the study was to evaluate the overall clinical efficacy of HCQ and TCZ in patients with COVID-19.</td>
<td>A total of 176 hospitalized patients with confirmed COVID-19 were included. Patients were divided into two comparative groups: (1) HCQ (n = 144) vs no-HCQ (n = 32) and (2) TCZ (n = 32) vs no-TCZ (n = 144).</td>
<td>There was no significant difference in in-hospital mortality in both HCQ and TCZ groups. On the 7th day of hospitalization of patients receiving TCZ, there was a significant reduction in CRP levels.</td>
<td>The use of HCQ and TCZ was not associated with a reduction of mortality in hospital, transition to intensive care, the need for IMV use, acute renal failure requiring dialysis, or hospital discharge. The lack of improvement in hard clinical outcomes suggests that large-scale, randomized trials are needed to evaluate the effectiveness of these drugs.</td>
</tr>
<tr>
<td>Paola Toniati, Simone Piva + associates</td>
<td>The assessment of intravenously administered Tocilizumab (TCZ) in COVID-19 treatment.</td>
<td>In the period from March 9 to March 20 at the university hospital Spedali Civili in Brescia (Italy) 100 more patients with severe COVID-19 pneumonia were treated with TCZ.</td>
<td>After 10 days, the condition of the respiratory system improved or stabilized in 77 (77%) patients, worsened in 23 (23%) patients, of which 20 (20%) died.</td>
<td>The effectiveness of TCZ must be confirmed in large clinical trials with randomized treatment.</td>
</tr>
<tr>
<td>Pan Luo, Yi Liu, Lin Qiu, Xiulan Liu, Dong Liu, Juan Li</td>
<td>Assessment of the effectiveness of tocilizumab (TCZ) therapy in patients with COVID-19.</td>
<td>This study recruited COVID-19 infected patients who were treated with TCZ from January 27 to March 5, 2020 in Zhongfuxincheng, Tongji Hospital in Wuhan, China.</td>
<td>The conducted studies have confirmed the effectiveness of TCZ in the prevention or treatment of hypercytokinemia (&quot;cytokine storm&quot;) caused by COVID-19. In most patients, the concentration of the acute phase reactator decreased and the patients returned to normal.</td>
<td>Further testing of COVID-19 patients is needed to document the effectiveness of TCZ.</td>
</tr>
<tr>
<td>RECOVERY Collaborative Group</td>
<td>Evaluation of the effect of tocilizumab in adult patients admitted to hospital with COVID-19 with both hypoxia and systemic inflammation.</td>
<td>In the period from April 23, 2020 to January 24, 2021, a study of the effectiveness of Tocilizumab therapy was conducted in one of 131 centers in the United Kingdom.</td>
<td>Allocation to the tocilizumab group was associated with a greater likelihood of discharge from hospital within 28 days (57% vs.50%). Mortality after 28 days of therapy was as follows: in the group with TCZ - 31% without TCZ - 35%.</td>
<td>In hospitalized hypoxic and systemic inflammatory COVID-19 patients, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the amount of respiratory support.</td>
</tr>
</tbody>
</table>
Researchers
Jesús Rodríguez-Baño,
Jerónimo Pachón, Jordi Carratalà,
Pablo Ryan, Inmaculada Jarrín, María Yllescas.1
José Ramón Arribas + associates

Aim
Evaluation of the relationship between the use of tocilizumab and the risk of intubation or death in patients with COVID-19.

Material and Methods
The study was carried out in 60 Spanish hospitals, 778 of which were COVID-19 patients. The primary outcome was intubation or death. The observation lasted 21 days.

Results
A total of 88 tocilizumab-treated patients were compared with 344 untreated patients. The primary endpoint occurred in 10 patients (11.4%). Tocilizumab was also associated with a lower risk of death in the IPTW analysis (0.07; 0.02–0.17; p <0.001).

Conclusions
Tocilizumab may improve the health of patients with COVID-19 and should be given priority in randomized trials.

At Abington - Jefferson Health Hospital in the United States, a study was conducted involving the adult patients (≥18 years old) hospitalized between March 1, 2020 and May 30, 2020. The diagnosis of COVID-19 was confirmed in all patients. The patients were divided into two comparative groups: (1) HCQ (n=144) vs no-HCQ (n=32) and (2) TCZ (n=32) vs no-TCZ (n=144). Six people died in the TCZ group, and 13 without TCZ. In the group of patients administered with HCQ, 13 people died, and in the control group - 6 people. There was no significant difference in the likelihood of death in hospital, transfer to intensive care, the need for invasive mechanical ventilation, acute renal failure requiring dialysis, or hospital discharge upon recovery in both the HCQ and TCZ groups compared to their control group (7). In Spedali Civili University Hospital in Brescia (Italy) from March 9 to March 20, TCZ was administered to 100 patients treated in the intensive care unit. 43 patients received TCZ in the intensive care unit (ICU) and 57 in the general unit because there were no beds available in the ICU. Tocilizumab was administered at a dose of 8 mg/kg. for two consecutive intravenous infusions 12 hours apart. The third infusion was optional regarding to clinical response. Of the 57 patients, 37 (65%) had suspended non-invasive ventilation (NIV) (median BCRSS: 1 [IQR0-2]), 7 (12%) patients remained constant in NIV, and 13 (23%) patients (10 died, 3 were admitted to the ICU) (Figure 2).

Figure 2. Comparison of TCZ - treated patients whose health improved, worsened, they died or admitted to the ICU in Spedali Civili University Hospital in Brescia (Italy)

Of the 43 patients treated in the intensive care unit, 32 (74%) (17 of them were disconnected from the ventilator and discharged), 1 (2%) (BCRSS: 5) and 10 (24%) died (all of them had BCRSS ≥ 7 before TCZ) (B) (Figure 3).
After 10 days, the respiratory system improved or stabilized in 77 (77%) patients, 61 of them showed significant removal of diffuse bilateral opacities on the X-ray chest and 15 of them were discharged. The respiratory system deteriorated in 23 (23%) patients, including 20 (20%) who died (8) (Figure 4).

From January 27 to March 5, 2020, at the Zhongfaxincheng campus at Tongji Hospital in Wuhan, China, 15 patients (12 men and 3 women) with COVID-19 were included in the study (9). The result of the therapy is presented in the chart below (Figure 5).
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Figure 5. Comparison of TCZ-treated patients whose health improved, worsened or they died in Tongji Hospital in Wuhan

In the period from April 23, 2020 to January 24, 2021, a study of the effectiveness of Tocilizumab therapy was conducted in one of 131 centers in the United Kingdom. Of the 21 550 patients enrolled in the study, 4 116 (19%) were excluded. 2 022 patients were randomized to tocilizumab and 2 094 were randomized to ordinary care, without tocilizumab. The mean age of the participants was 63-66 years old (10) (Table 4).

Patients assigned to tocilizumab were to receive the drug as a single intravenous infusion over 60 minutes. The dose of tocilizumab was based on body weight (800 mg if weight > 90 kg; 600 mg if weight > 65 and ≤90 kg; 400 mg if weight > 40 and ≤65 kg; and 8 mg / kg, if body weight ≤40 kg). The second dose could be administered 12-24 hours later if, in the opinion of the attending physician, the patient’s condition had not improved (10).

Table 4. Comparison of TCZ treated patients who were discharged from hospital without improving or who died in one of 131 hospitals in the UK

<table>
<thead>
<tr>
<th></th>
<th>Patients treated with TCZ (n=2022)</th>
<th>Patients not treated with TCZ (n=2094)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>621 (31%)</td>
<td>729 (35%)</td>
</tr>
<tr>
<td>Discharged from hospital within 28 days</td>
<td>1150 (57%)</td>
<td>1044 (50%)</td>
</tr>
<tr>
<td>Patients with no improvement in health</td>
<td>251 (12%)</td>
<td>321 (15%)</td>
</tr>
</tbody>
</table>

Assigning use to tocilizumab was associated with a greater likelihood of discharge from hospital within 28 days (57% vs.50%). Mortality after 28 days of therapy was as follows: in the group with TCZ - 31%, without TCZ – 35% (10).

Another study was conducted in 60 Spanish hospitals. The study included 778 patients with COVID-19 and with clinical and laboratory data indicating inflammation. The primary outcome was intubation or death - follow-up was 21 days. A total of 88, 117, 78 and 151 patients treated with tocilizumab, IHDC, PDC, and combination therapy, respectively, were compared to 344 untreated patients. The primary endpoint occurred in 10 (11.4%), 27 (23.1%), 12 (15.4%), 40 (25.6%) and 69 patients (21.1%), respectively. The risk factors based on IPTW (odds Ratio for combination therapy) for the primary endpoint were 0.32 (95% CI 0.22-0.47; p <0.001) for tocilizumab, 0.82 (0.71-1.30; p 0.82) for IHDC, 0.61 (0.43–0.86; p 0.006) for PDC and 1.17 (0.86–1.58; p 0.30) for combination therapy. Tocilizumab was also associated with a lower risk of death in the IPTW analysis (0.07; 0.02–0.17; p <0.001) (11).

The above analysis shows that TCZ added to the standard treatment reduces the mortality rate of COVID-19 patients. In each study, more than half of the ICU patients improved their health (Table 5).
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<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeming Wang, MD, Dingyu Zhang + associates</td>
<td>Assessment of Remdesivir effectiveness on COVID-19 patients</td>
<td>The study was conducted at ten hospitals in Hubei, China. Eligible patients were adults (≥ 18 years of age) admitted to hospital with laboratory-confirmed infection with SARS-CoV-2.</td>
<td>Remdesivir reduces the duration of invasive mechanical ventilation in patients with COVID-19.</td>
<td>This dosing regimen with intravenous Remdesivir was found to be well tolerated but did not provide a significant health changes in critically ill COVID-19 patients, but improvement in some clinical parameters. There is a need to confirm Remdesivir in large clinical trials.</td>
</tr>
<tr>
<td>Jonathan Grein, Norio Ohmagari + associates</td>
<td>Assessment of Remdesivir effectiveness on COVID-19 patients</td>
<td>The study included patients with confirmed SARS-CoV-2 who had an oxygen saturation of 94% or less while breathing unassisted or who were receiving oxygen support. Patients received a 10-day course of remdesivir consisting of 200 mg intravenously administered on day 1 followed by 100 mg daily for the remaining 9 days of treatment.</td>
<td>Improvement was seen in 36 of 53 patients (68%) and 7 of 53 patients (13%) died after finishing the treatment.</td>
<td>In patients hospitalized for severe Covid-19 treated with Remdesivir, clinical improvement was observed in 36 out of 53 patients (68%). The assessment of effectiveness requires further research.</td>
</tr>
<tr>
<td>Zeno Pasquini, Roberto Montalti, Chiara Temperoni, Benedetta Canovari, Mauro Mancini, Michele Tempesta, Daniela Pimpini, Nicoletta Zallocco, Francesco Barchiesi</td>
<td>Assessment of Remdesivir effectiveness on COVID-19 patients committed to mechanical ventilation</td>
<td>This study includes patients undergoing mechanical ventilation with confirmed SARS-CoV-2 infection admitted to the ICU at Pesaro Hospital between February 29 and March 20, 2020.</td>
<td>Twenty patients completed the 10-day treatment successfully and five (20%) died.</td>
<td>This study confirmed that the mortality rate of patients with COVID-19 undergoing mechanical ventilation is high. The use of remdesivir has a positive effect on the condition of patients with COVID-19.</td>
</tr>
<tr>
<td>Christoph D. Spinner, Robert L. Gottlieb, Dr Gerard J. Criner, José Ramón Arribas López + associates</td>
<td>Evaluation whether remdesivir provide benefits for the clinical status of hospitalized patients with moderate COVID-19 disease?</td>
<td>582 people were qualified for the study; 193 started a 10-day remdesivir cycle, 191 patients started a 5-day remdesivir cycle, and 200 continued standard care.</td>
<td>After the end of therapy, 125 people were discharged from the hospital, which constituted 65% of patients with 10 days of remdesivir treatment. 134 patients (70%) who were in the 5-day cycle were discharged from the hospital, and 120 (60%) patients receiving standard treatment were discharged from the hospital.</td>
<td>Patients randomly assigned to the 5-day cycle of remdesivir had a statistically significant difference in clinical status compared to standard of care.</td>
</tr>
</tbody>
</table>
Remdesivir therapy is also used to treat COVID-19. The first study was conducted at ten hospitals in Wuhan, Hubei (China). In a period from February 6, 2020 to March 12, 2020, 237 patients were enabled and randomized to groups (158 to remdesivir and 79 to placebo). Adverse reactions were reported in 102 (64%) of 155 patients in the remdesivir group and 50 (64%) of 78 in the control group. The 28-day mortality was similar in both groups 22 (14%) deaths in the remdesivir group vs 10 (13%) in the placebo group). The rates of clinical improvement on days 14 and 28 were not significantly different between the groups but were numerically higher in the remdesivir group than in the placebo group. In patients assigned to the remdesivir group, the duration of invasive mechanical ventilation did not differ significantly, but was shorter than in patients in the control group. However, the number of patients with invasive mechanical ventilation was small (12). 61 patients received at least one dose of remdesivir on or before March 7, 2020, 8 of these patients were excluded. Of the 53 patients left mentioned in analysis 75% received a full 10 day course of remdesivir, 10 (19%) 5 to 9 days of treatment and 3 (6%) less than 5 days of curing. During median follow-up 18 days after receiving the first dose of remdesivir, 36 of 53 patients (68%) showed improvement in the oxygen support category, while 8 of 53 patients (15%) has shown deterioration. The improvement was seen in 12 patients, who either breathed by the air or received an additional oxygen with low airflows. In this group of hospitalized patients suffering from COVID-19, clinical improvement was observed in 36 out of 53 patients (68%), and 7 out of 53 patients (13%) died after completion of hospital treatment (13).

In the period from February 29 to March 20, 2020, 51 patients were enrolled, including, 25 treated with remdesivir. 20 patients completed 10 days of treatment with a positive result, and 5 (20%) died (14). At the Luigi Sacco hospital in Milan, Italy, from February 23 and March 20, 2020, 35 patients were enrolled in the study, including 18 in the intensive care unit (ICU) and 17 in the infection diseases ward (IDW). The 10 day course of remdesivir was completed by 22 patients, (63%) and discontinued in -13, of whom eight (22.8%) discontinued treatment due to adverse events (15). The median follow-up was 39 days. On day 28, 14 (82.3%) patients in IDW were discharged, two were still hospitalized, and one died (5.9%), while in the ICU, 6 (33.3%) were discharged, 8 (44.4%) of the patients died, three (16.7%) were still mechanically ventilated, and one (5.6%) – health has improved (15) (Figure 6).

![Figure 6. Comparison of Remdesivir-treated patients whose health improved, they died, checked out or no change in Luigi Sacco hospital in Milan, Italy](image-url)
Table 6. Comparison of Remdesivir treated patients who were discharged from hospital without improving or who died

<table>
<thead>
<tr>
<th></th>
<th>10-Day remdesivir (n = 193)</th>
<th>5-Day remdesivir (n = 191)</th>
<th>Standard care (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Death</td>
<td>2 (1%)</td>
<td>0</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>2: Hospitalized, requiring invasive mechanical ventilation</td>
<td>1 (1%)</td>
<td>0</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>3: Hospitalized, requiring non-invasive ventilation</td>
<td>0</td>
<td>5 (3%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>4: Hospitalized, requiring supplemental low flow oxygen</td>
<td>12 (6%)</td>
<td>7 (4%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>5: Hospitalized, does not require additional oxygen, but requires constant medical care</td>
<td>44 (23%)</td>
<td>38 (20%)</td>
<td>46 (23%)</td>
</tr>
<tr>
<td>6: Hospitalized, requiring no additional oxygen or medical care</td>
<td>9 (5%)</td>
<td>7 (4%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>7: Discharged from the hospital</td>
<td>125 (65%)</td>
<td>134 (70%)</td>
<td>120 (60%)</td>
</tr>
</tbody>
</table>

In a study that ran from March 15 to April 18, 2020, in 105 hospitals in the United States, Europe, and Asia. 612 patients participated and were assessed for eligibility for remdesivir therapy. 582 people were qualified; 193 started a 10-day cycle of remdesivir, 191 patients started a 5-day cycle of remdesivir, and 200 continued standard care. Remdesivir was administered intravenously at a dose of 200 mg on day 1 followed by 100 mg / day. After the end of therapy, 125 people were discharged from the hospital, which constituted 65% of patients treated with 10 days of remdesivir treatment. 134 patients (70%) who were in the 5-day cycle and 120 (60%) patients receiving standard treatment were discharged from the hospital respectively (16) (Table 6).

Taking into account the findings on remdesivir, it may have a beneficial effect on SARS-CoV-2 pneumonia, especially in patients who are not critically ill. Remdesivir may shorten recovery time in hospitalized adults suffering from severe disease caused by COVID-19 (16).

Table 7. Amantadyna – The results of the analysis of individual articles

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Aim</th>
<th>Material and Methods</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalo Emiliano Aranda-Abreu, José D. Aranda-Martínez, Ramiro Araújo, María Elena Hernández-Anguil, Deissy Herrera-Covarrubias, and Fausto Rojas-Durán</td>
<td>Is amantadine an effective antiviral drug that can stop the symptoms of the coronavirus and give the body an opportunity to defend itself by generating protective antibodies.</td>
<td>Fifteen people with COVID-19 symptoms were administered amantadine for a period of 14 days.</td>
<td>Amantadine has shown its effectiveness as patients recovered without being in hospital.</td>
<td>Amantadine can be used as a viable and cost-effective alternative in the treatment of people with severe acute respiratory syndrome (COVID-19)</td>
</tr>
<tr>
<td>Wlodzimierz Bodnar, Gonzalo Aranda-Abreu, Monika Slabon-Willand, Sylwia Kotecka, Małgorzata Farnik, Jarosław Bodna</td>
<td>The aim of the study was an observational, single-center analysis of confirmed COVID-19 cases treated with amantadine on an outpatient basis.</td>
<td>55 patients with a confirmed diagnosis of COVID-19 were treated with amantadine on an outpatient basis. The analysis was based on symptoms, hospitalization, and number of deaths.</td>
<td>93% (n = 51) of patients did not require hospitalization during treatment.</td>
<td>Data show that amantadine hydrochloride is effective in preventing hospitalization and death in COVID-19 patients.</td>
</tr>
</tbody>
</table>

Amantadine is another form of therapy in patients with COVID-19. In the period from April 1 to July 25, 2020 (17). An observational study was carried out using the questionnaire on the symptoms of the disease as well as chronic diseases of 15 patients from the southeastern area of Mexico with symptoms of COVID-19 who have been treated with the antiviral amantadine. The patients were treated on an outpatient basis with 100 mg of amantadine (one tablet in the morning and one in the afternoon) for a period of 14 days. This drug has shown its effectiveness as patients recovered with the treatment without having to go to the hospital for mechanical ventilation. All patients developed IgG antibodies to COVID-19 (18).
55 patients with a confirmed diagnosis of COVID-19 were treated with amantadine on an outpatient basis with a treatment regimen ranging from 200 mg to 500 mg per day. Most of the patients, 64% (n = 35) with comorbidities and 53% (n = 29) of patients were diagnosed with pneumonia, none of them died, and only 4 required hospitalization for COVID-19. Stable health was achieved in 91% (n = 50) of patients within 48 hours after the first dose of amantadine with further improvement. Overall, 93% (n = 51) of patients did not require hospitalization during treatment (19). Amantadine is effective in preventing hospitalization and death in COVID-19 patients (Table 7).

Effective forms of therapy for patients after COVID-19

Many people with COVID-19 disease have various problems with the proper functioning of the respiratory, circulatory and nervous systems. Therefore, they require rehabilitation to mitigate the effects of the infection (5, 20).

Several studies have been conducted to prove that different types of rehabilitation are a necessary factor in the recovery process. One of them was carried out at Hainan General Hospital Central Hospital and Huanggang Central Hospital, where from January 1, 2020 until February 6, 2020, 72 participants were enrolled, of which 36 patients underwent pulmonary rehabilitation (2 sessions a week for 6 weeks and once a day for 10 minutes), and another 36 did not undergo any rehabilitation interventions. After 6 weeks of pulmonary rehabilitation, significant differences were found in the parameters FEV1 (L), FVC (L), FEV1 / FVC%, TLCO% and 6-minute exercise tests in the rehabilitation group (21) (Table 8).

Table 8. Comparison of lung function test results after and before rehabilitation (21)

<table>
<thead>
<tr>
<th>Intervention group (n = 36)</th>
<th>Control group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Lung function test</td>
<td></td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.10 ± 0.08</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.79 ± 0.53</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>60.48 ± 6.39</td>
</tr>
<tr>
<td>TLCO %</td>
<td>60.3 ± 11.3</td>
</tr>
<tr>
<td>Exercise capacity test</td>
<td></td>
</tr>
<tr>
<td>6MWT .m</td>
<td>162.7 ± 72.0</td>
</tr>
</tbody>
</table>

* Compared to the same group after intervention, P <0.05.
# Compared to the intervention control group, P <0.05.

Research results show that six-week pulmonary rehabilitation improves respiratory function after COVID-19.

Another form of therapy after COVID-19 is BFHX, which can have a strong rehabilitation effect on physiological activity in patients recovering from COVID-19, which in turn can alleviate symptoms of fatigue and improve exercise tolerance (22).

From May 4 to June 21, 2020, 352 patients discharged after COVID-19 treatment at five university hospitals in China were screened, and 131 patients were enrolled in the study. All participants were assigned randomly to BFHX (n = 66) and placebo (control group, n = 65). Two patients were not taking the medication. A total of 129 patients were enrolled in the study. BFHX or placebo was administered orally three times a day (1.4 g / dose) for 90 days. The primary outcomes were the assessment of improvements in exercise tolerance and chest computed tomography (CT). After 3 months of treatment, the BFHX group showed greater attenuation of chest CT pneumonia lesions than the placebo group (P <0.05). The improvement in 6-minute walking distance (6MWD) from baseline was also significantly better in the BFHX group than in the placebo group (P <0.01). The incidence of adverse events was higher in the BFHX group than in the placebo group (9.38% vs 4.62%), the difference was not significant (P = 0.3241) (22).

A study was conducted at First Affiliated Hospital of Nanchang University, First People’s Hospital of Nanchang, and Xinyu People’s Hospital to investigate the effects of Liu Zi Jue exercise on discharged from hospital COVID-19 patients. 33 patients took part in the study - they were discharged from the hospital after COVID-19. Enrolled individuals were instructed to practice the Liu Zi Jue exercise routine once a day for 20 minutes for 4 weeks. Data was measured before and after the interventions. After 4 weeks: the patients’ maximum inspiratory pressure (MIP), peak inspiratory flow (PIF) and deep breathing diaphragm movement (DM-DB) increased significantly. The breathlessness was relieved. In terms of the quality of life, exercise capacity increased and significantly alleviated depression and anxiety in patients (23).
Many specialists in various articles, in addition to pulmonary rehabilitation, also recommend physical activity under the supervision of a physiotherapist, for example resistance training in case of muscle weakness and exercise rehabilitation to improve coordination and other physical functions.

In addition to physical rehabilitation, psychological support is also recommended to reduce depression, stress, post-traumatic stress disorder (PTSD), and anxiety in patients with COVID-19 (22).

**Discussion**

Scientific research shows more and more information about COVID-19 and how to manage those who are infected and sick.

The first therapy that can be considered effective and supported in the latest research is tocilizumab (TCZ) therapy. TCZ is a recombinant humanized anti-interleukin 6 (IL-6R) monoclonal antibody used in the treatment of rheumatoid arthritis. Studies show that TCZ given to patients with severe COVID-19 can be an effective treatment to reduce mortality. By neutralizing the key inflammatory factor in cytokine release syndrome (CRS), reduces the severity of the disease. No side effects have been reported in other studies, but it is recommended that rivaroxaban and apixaban should not be used in people receiving tocilizumab (7,9,24-28).

Remdesivir is a multi-targeted antiviral medicament against several virus families that is used to treat Ebola, but has also been shown to be active against SARS-CoV-2. It was identified at the start of the pandemic as being effective against COVID-19. Summarizing the above data analysis, treatment with remdesivir may have a beneficial effect on SARS-CoV-2 pneumonia, especially in patients who are not in critical condition. But like any drug, it can have an adverse effect. The most common are constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia and an increased list of bilirubin. (4,12-13,15,29-38)

Understanding the epidemiology and transmission dynamics of an emerging infectious disease is key to successful outbreak control. As the COVID-19 pandemic continues to spread rapidly across continents, more research is needed, focusing on treatment strategies for the infected people (39).

Amantadine is a dopaminergic drug, which means that it increases extracellular dopamine levels. This happens by increasing its release and by blocking the reuptake of this neurotransmitter. Amantadine is also a low affinity N-methyl-D-aspartate (NMDA) glutamate receptor antagonist with antiviral activity. It inhibits virus replication in the Vero E6 cell system. Amantadine is widely used as a symptomatic treatment to relieve fatigue, Parkinson's symptoms and help with the early symptoms of COVID-19 (17,40-41).

Understanding the epidemiology and transmission dynamics of an emerging infectious disease is key to successful outbreak control. As the COVID-19 pandemic continues to spread rapidly across continents, more research is needed, focusing on treatment strategies for the infected people (42-45).

People who have had COVID-19 often face other symptoms, such as shortness of breath, muscle aches and fatigue. They require further convalescence in the form of various forms of rehabilitation. In order for it to be implemented, it must be personalized, especially for patients with comorbidities, the elderly, those with obesity, multiple comorbidities and their complications (46).

**Conclusion**

The results of the analysed carried out studies clearly show that none of the forms of therapy developed so far is 100% effective in the treatment of COVID-19. In presented surveys, some promising medicaments that could be used in routine treatment were described. A small number of articles and research groups indicate the need for more research regarding the effects of pharmaceuticals on COVID-19 patients and to confirm that the symptoms presented in the review are caused by a virus and not related to another infection. It forms the basis for conduction further publications on this topic.

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