

Comparison of effectiveness of various treatment strategies in COVID-19 patients: A Systematic Review

Muhammad Shehryar Hussain¹, Ali Haider², Usama Ahmad Yousuf³, Warisha Laraib⁴, Fatima Dildar⁵,
Hafiz Amjad Hussain⁶

^{1,3} 3rd Year MBBS student, Allama Iqbal Medical College, Lahore.

⁴ 2nd Year MBBS student, CMH Lahore Medical College, Lahore.

^{2,5} 4th Year MBBS student, Allama Iqbal Medical College, Lahore.

⁶ Assistant Professor, Department of Medicine, Punjab Medical College, Faisalabad.

Author's Contribution

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^{5,6} Critical Review

Corresponding Author

Dr. Muhammad Shehryar Hussain

3rd Year MBBS student,

Allama Iqbal Medical College,
Lahore.

Email: shehryar1032@gmail.com

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Abstract

Background: The purpose of this study is to systematically review the effectiveness of various drugs and therapies by assessing already conducted studies on COVID-19 patients.

Methods: The eligibility criterion for this systematic review was to include the observational and experimental studies including case reports; conducted on the possible treatments of COVID-19. Only those studies were included that were written in the English language either published or unpublished from December 2019 to April 10, 2020. Quality of articles was assessed and flawed studies were excluded based on incomplete outcome data. Treatment strategies experimented on animals or those assessed through artificial intelligence were also excluded. The databases searched were PubMed, Google Scholar, Cochrane Library, and bioRxiv. The last date to search the databases was April 10, 2020.

Results: We selected 25 articles which include 12 case studies, 10 retrospective studies, one randomized controlled trial, one non-randomized Controlled trial, and one prospective observational study. Hydroxychloroquine proved to be effective in all three studies under consideration especially when it was used in a combination with azithromycin. Antivirals showed significant results in eleven out of sixteen studies. The remaining five studies showed antiviral therapy to be ineffective. Lopinavir/ritonavir did not show satisfactory results in most of the COVID-19 patients. Both of the studies regarding convalescent plasma therapy showed significant improvement in patients undergoing treatment. Two studies regarding treatment with immunoglobulins also showed good results. A study on the use of Mesenchymal stem cell transplant for treatment of COVID-19 patients also proved to be effective. Likewise, a study on the use of Traditional Chinese Medicine along with Western Medicine also showed good results. In patients of organ transplant, withdrawal of immunosuppressive drugs, and the use of methylprednisolone along with antivirals had shown significantly good results. Among all these therapeutic approaches we found convalescent plasma therapy to be most effective.

Conclusion: So far, a small number of studies have been conducted on the treatment of COVID-19 patients and most of them were conducted on the Chinese population. More randomized controlled trials are needed to evaluate the effectiveness of different treatment strategies at a broader level.

Keywords: COVID-19 treatment, SARS-COV-2, convalescent plasma therapy, Lopinavir/ritonavir, Hydroxychloroquine, and azithromycin, Remdesivir, COVID-19 serum therapy.

Introduction

In December 2019, a virus named "Severe acute respiratory syndrome corona virus-2" (SARS-COV-2 or COVID-19) infected people in China causing fever, dry cough, shortness of breath and pneumonia.¹ Virus can be transmitted from one human to another.² Now this mass killer infection is a pandemic around the world. This virus (COVID-19) has infected 1,684,833 people, among them 375,499 people have recovered and 102,136 people have died till April 10, 2020. Many studies have been conducted around the world to devise an effective treatment for COVID-19. Investigational drugs anti-virals, antimalarials, anti-inflammatory, Traditional Chinese Medicine, plasma technique, immunotherapies, and investigational vaccines are all the strategies applied for the management and treatment of COVID-19 around the globe. Our study systematically reviews the studies on the previously mentioned drugs and techniques and compares the effectiveness of different treatment strategies for COVID-19 in humans. The case reports describing the treatment strategies of patients having any comorbidity along with COVID-19 were also reviewed.

Methods

The eligibility criterion for this systematic review was to include the observational and experimental studies including case reports conducted on the possible treatments of COVID-19. Only those studies were included that were written in the English language either published or unpublished from December 2019 to April 10, 2020. The databases searched were PubMed, Google Scholar, Cochrane Library, and bioRxiv. The last date to search the databases was April 10, 2020. The search terms used were COVID-19 treatment, hydroxychloroquine, and azithromycin for COVID-19 treatment, Anti-malarial for COVID-19 treatment, Antivirals for COVID-19 treatment, Serotherapy for COVID-19. Three reviewers individually searched the databases. At first step, reviewers selected the studies by reading the titles and abstracts, and those studies were selected which were related to the treatment of COVID-19. At the second step, three reviewers together removed the duplicates

and rechecked the studies by consulting the full texts if needed and removed the articles which were not eligible. In the third step, the quality of articles was assessed and flawed studies were excluded based on incomplete outcome data after full-text review. Treatment strategies experimented on animals or those assessed through artificial intelligence were excluded. Studies having full-text articles in languages other than English were also excluded. Data extraction was done by three authors individually and rechecked by one author. The variables used for data extraction were the type of study, number of individuals, possible treatment with applied dose, and any comorbidity.

Results

We searched four research libraries and found 1121 relevant articles. 25 articles were found eligible for our study after removing duplicates, checking titles, abstracts, and full text. These 25 articles were finalized based on previously decided inclusion and exclusion criteria. The 25 selected articles include 12 case studies, 10 retrospective studies, one randomized controlled trial, one non-randomized Controlled trial, and one prospective observational study. The column labeled as "**COVID-19 Specific Treatment**" contains the therapies that were used by the authors in their studies for targeting the COVID-19 virus specifically. Dosage and duration of use of these therapies are mentioned in the "**Dosage and Duration**" column. The column under the heading of, "**Adjunct Treatment**" includes drugs and therapies used for supportive treatment, superadded infections, and comorbidities. It also includes other drugs used for COVID-19 along with the COVID-19 specific treatment. The column under the heading of "**Treatment Category**" includes drugs and therapies which are classified as Anti-malarial, Anti-inflammatory, Traditional Chinese Medicine, Corticosteroids, Anti-viral, Immunoglobulin therapy, Convalescent Plasma therapy, Mesenchymal Stem cell transplant therapy. Hydroxychloroquine showed remarkable results in all the above studies. Moreover, when a combination of hydroxychloroquine and azithromycin was used, even better results were observed. (Table 1&2)

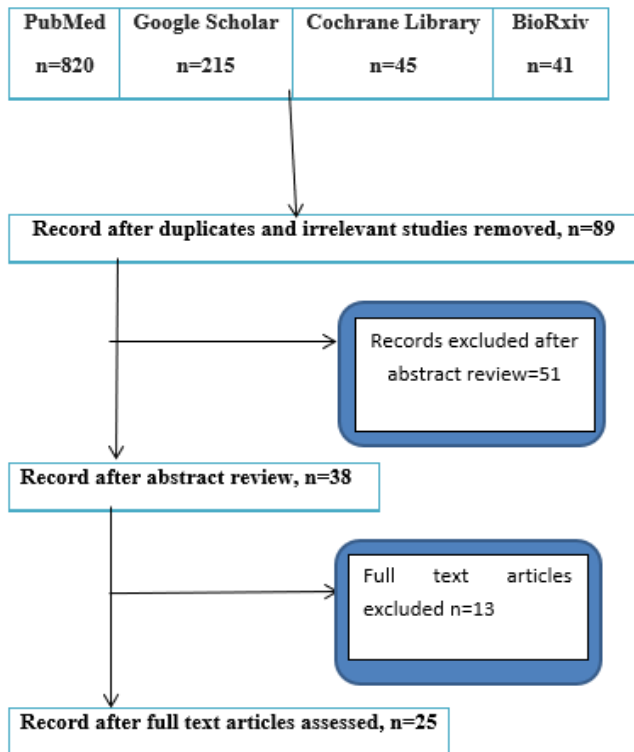


Figure 1: Study selection design

Table 1: Hydroxychloroquine usage

ARTICLE	TYPE OF STUDY	NUMBER OF INDIVIDUALS	DOSAGE AND DURATION (COVID 19 SPECIFIC TREATMENT)	COMORBIDITY	ADJUNCT TREATMENT	OUTCOME	TREATMENT CATEGORY
Gautret et al [3]	non-randomized controlled trial	Total patient=36	hydroxychloroquine	N/A	Azithromycin	70% cured	Antimalarial drug
Gautret et al[10]	Prospective Observational study	Eighty patients	Hydroxychloroquine sulfate /Azithromycin	Hypertension Diabetes Chronic respiratory disease	Ceftriaxone	Improvement observed in all patients except one 86 year old patient who died.	Antimalarial + Anti-Inflammatory

Table 2: Case Study of HYDROXYCHLOROQUINE

ARTICLE	COVID19 SPECIFIC TREATMENT	OUTCOME
Mukherjee et al [6]	Hydroxychloroquine	Hydroxychloroquine showed significantly good results after 3 days of treatment.

Table 3: Antivirals

ARTICLE	TYPE OF STUDY	NUMBER OF INDIVIDUALS	COVID 19 SPECIFIC TREATMENT	COMORBIDITY	ADJUNCT TREATMENT	OUTCOME	TREATMENT CATEGORY
Wang et al [4]	Retrospective study	Four patients	Lopinavir Arbidol	Fatty liver in one patient only	Antibiotic supplement oxygen	3 patients showed significant improvement	Antivirals+ Traditional Chinese medicine
Cheng et al [5]	Retrospective study	5 patients	Shufeng Jiedu Capsule Lopinavir /Ritonavir	N/A	N/A	1 pt. showed slight improvement LPV/r didn't reduce the timing of COVID-19 shedding	Antiviral
Zheng et al [7]	Retrospective study	Total patient=55	Arbidol tablets /Ribavirin / Recombinant Interferon-α2b/ Traditional Chinese medicine (TCM)	N/A	low-flow oxygen therapy / Corticosteroids	45 pts. Discharged No pt died during this treatment	Antivirals / corticosteroids
Wang et al [26]	Retrospective study	Total =138 patients	Oseltamivir	Hypertension / Diabetes/ cardiovascular disease/ cerebrovascular disease	Antiviral therapy / Glucocorticoid therapy/ kidney replacement therapy/ Oxygen inhalation/ noninvasive ventilation /Methylprednisolone Antibacterial Moxifloxacin hydrochloride /Immunoglobulin/Thymalfasin /High-flow nasal oxygen therapy	No significant result Six patient died in ICU group and many are still hospitalized	Antivirals
Chen et al [27]	Retrospective study	Total=9 patients	Interferon alfa-2b/Lopinavir and ritonavir/ Methylprednisolone/ Traditional Chinese medicine	N/A	Moxifloxacin hydrochloride /Immunoglobulin/Thymalfasin /High-flow nasal oxygen therapy	Significant recovery with combined treatment of Chinese and western medicine	Antivirals+ corticosteroids+ traditional Chinese medicine

Table 4: Case Study of Patients with History Organ Transplant

ARTICLE	COVID19 SPECIFIC TREATMENT	COMORBIDITY	ADJUNCT TREATMENT	OUTCOME
Zhu et al [21]	Umifenovir Interferon α Methylprednisolone	Kidney transplant 12 years back	Moxifloxacin / Intravenous immunoglobulin /Biapenem /Pantoprazole /Cessation of immunosuppressive therapy Prednisone (Pred)	Patient discharged after a successful recovery
Bin et al [22]	Umifenovir combined with Lopinavir/ritonavir /Alpha	Liver transplant therapy two and half year back	Intravenous immunoglobulin Prophylactic antibiotic Oxygen therapy Immunosuppressive drug	Patient discharged after a successful recovery

	interferon/Systemic methylprednisolone		<i>withdrawal</i>	
Chen et al [20]	Umifenovir Ribavirin Methylprednisolone (MP)	kidney transplant 6 years back	Moxifloxacin	Reduce in the immunosuppressant intake and slight intake of Methylprednisolone show significant benefit

Table 5: Case Study of Patients with no Comorbidity

ARTICLE	COVID19 SPECIFIC TREATMENT	OUTCOME
Lim et al [23]	Lopinavir/ritonavir	Viral load of beta coronavirus started to decrease after administration of Lopinavir/ritonavir
Holshue et al [24]	Intravenous Remdesivir	The patient showed significant improvement after intravenous Remdesivir dose
Xu et al [25]	Lopinavir/ ritonavir Interferon alfa-2b	Temperature reduced but no significant betterment in cough, dyspnea, and fatigue. In the end, the patient died due to cardiac arrest.

Table 6: Case Study of Patients with no Comorbidity

ARTICLE	TYPE OF STUDY	NUMBER OF INDIVIDUALS	COVID 19 SPECIFIC TREATMENT	COMORBIDITY	ADJUNCT TREATMENT	OUTCOME	TREATMENT CATEGORY
Shen et al [19]	Case series	Five patients (critically ill)	Convalescent Plasma	One patient had hypertension and Mitral valve insufficiency	All patients received Mechanical ventilation Antiviral agents Methylprednisolone	Ct value becomes negative on post-transfusion Day 1 for one patient Day 3 for two patients Day 12 for two patients	Convalescent Plasma
Zhang et al [8](1)	Case series	Four patients	Convalescent Plasma	Hypertension /Bacterial and Aspergillus co-infection/Chronic obstructive pulmonary disease/Hypertension and chronic renal failure/Gram-positive bacterial infection	Arbidol Lopinavir-ritonavir Interferon-alpha inhalation Oseltamivir Ribavirin	All patients showed significant recovery	Convalescent plasma +Antivirals

Table 7: Immunoglobulin

ARTICLE	TYPE OF STUDY	NUMBER OF INDIVIDUALS	COVID 19 SPECIFIC TREATMENT	COMORBIDITY	ADJUNCT TREATMENT	OUTCOME	TREATMENT CATEGORY
Zhang et al [11]	Case study	Two patients	Gamma globulin and hormones	N/A	Antibacterial drugs Oseltamivir and Abidol hydrochloride Tanning.(Chinese herbal medicine)	Both patients showed significant recovery	Gamma globulin and hormone
Cao et al [15]	Case study	Three patients	Intravenous Ig	Hypertension	Supplemental oxygen/ Moxifloxacin/Valsartan / Lelodipine/ Lopinavir/ritonavir/Methylprednisolone	The patient became afebrile and discharged day	Intravenous Ig

Table 8: Mixed Therapies

ARTICLE	TYPE OF STUDY	NUMBER OF INDIVIDUALS	COVID 19 SPECIFIC TREATMENT	COMORBIDITY	ADJUNCT TREATMENT	OUTCOME	TREATMENT CATEGORY
Leng et al [13]	Retrospective study	Total=10 patient	Mesenchymal Stem Cells transplant	One patient had hypertension	N/A	4/7 patients discharged 3/7 patients were in stable condition and showed significant improvement	Mesenchymal Stem Cells transplant
Deng et al [16]	Case study	One patient	Herbal drugs for increase of lymphocyte count and for fever	Chronic anemia	α-interferon/ Levofloxacin /Oxygen supplement/ Human immunoglobulin pulse therapy for three	Significant outcome and patient recovered	Traditional Chinese medicine

No significant improvement was seen in patients receiving Lopinavir/ritonavir alone. However, when Interferon or Ribavirin was used along with Lopinavir/ritonavir a significant improvement was noticed in the above studies. Interferon and Ribavirin when used in combination without other antivirals also proved to be effective. Patients receiving Traditional Chinese medicine along with Lopinavir/ritonavir also showed significant improvements. Arbidol proved to be effective when used alone for patients of COVID-19. Oseltamivir when used alone did not prove to be effective.

Intravenous Remdesivir also showed good results but requires testing on a large scale.(Tables 3-5) .

All patients receiving Convalescent Plasma Therapy showed significant improvements and a decrease in viral load after infusion of plasma in above-mentioned studies (Table 6). All patients who received Immunoglobulin Therapy became afebrile and showed significant improvements (Table 7)

Patients receiving Mesenchymal Stem Cell Therapy showed far better results than the control group receiving placebo. The patients receiving MSC became stable and were discharged from the hospital later on.

Traditional Chinese medicine also showed good results when used with western medicine but it should not be used as a single treatment modality for COVID 19 patients (Table 8).

Additional Recommendations

COVID-19 belongs to a family of beta coronavirus and has enveloped positive sense ribonucleic acid and attacks one main site for entry into cells. That site is an ACE2 receptor and the other thing responsible is a cellular serine protease TMPRSS2 protein required for HCoV-19 spike protein priming. Most of the body tissues which are abundant with ACE2 receptor (like myocardial tissue, alveolar type 2 cells in lungs and capillary endothelium, etc.) are severely affected by this virus. Another important way that it affects the body is by manipulating the body to release abundant inflammatory substances like interleukins and tumor necrosis factor to generate a cytokine storm which causes septic shock and multiple organ failure leading to death.¹³ Since there is no vaccine or specific drug for treatment, our best weapon against it would be drugs that prevent the virus to get attached to ACE2 receptors or ACE2 inhibitors/blockers or drugs or treatments that prevent a cytokine response. Drugs that decrease viral load to stop viral shedding by an infected person are also the need of the hour. We will be discussing drugs that have undergone clinical trials and can be a potential treatment for COVID-19.

Chloroquine phosphate and Hydroxychloroquine sulfate are very effective in decreasing the viral load of infected patients and alleviating their symptoms. They have been shown to have decreased the average duration of stay of infected people in hospitals and improved CT scan results and decreased viral load in patients in China. Hydroxychloroquine alters the pH of the cell membrane and prevents the fusion of the virus with host cells. It inhibits viral protein and nucleic acid replication and release of the virus. It also suppresses TNF alpha and IL-6.⁶ However, these results were observed with a specific dose of these drugs but were not observed below that dose. Since hydroxychloroquine is more effective than chloroquine and has fewer toxic effects and less interaction with other drugs that is why it is being preferred to chloroquine.³ Hydroxychloroquine has been used in combination with other drugs like azithromycin and antivirals so its effects, when used alone in patients, are still unknown and demand clinical studies[3,10]. Chloroquine and

Hydroxychloroquine have been shown to prolong QTc interval which may cause arrhythmias.²⁸

Azithromycin has been used in combination with a couple of drugs for treating COVID-19 patients most commonly with Hydroxychloroquine and Antivirals and has shown good results. Viral load in patients receiving Hydroxychloroquine and Azithromycin combination showed a dramatic decrease when confirmed by PCR and Culture technique.^{3,10} Since Azithromycin has been commonly used by people for infections, there are very few chances of drug toxicity or intolerance to develop.¹⁰ Azithromycin has been shown to prevent respiratory tract infections when given to patients of viral infections.³ However, Azithromycin is contraindicated in pregnant females.²⁹

Lopinavir/ritonavir (LPV/r) had shown excellent results while treating SARS infection back in 2003. However, trials of lopinavir/ritonavir on COVID-19 patients have not been satisfactory and suggest no satisfactory decrease in viral load.^{5,9} The patients receiving lopinavir/ritonavir had the same duration of stay in hospitals as the patients who received standard therapy. There were no significant improvements in CT scans of the lungs. LPV/r did not reduce the duration of viral shedding in patients.^{5,9} Moreover, the group receiving LPV/r had more gastrointestinal side effects like nausea, vomiting, and diarrhea as compared to the group receiving standard therapy.⁹ However, patients with LPV/r therapy had a shorter stay in ICU as compared to the group receiving standard therapy. Hospital discharge was early in the LPV/r group with a difference of 1 day. In a clinical study percentage of patients showing improvements was higher in LPV/r group (45.5%) as compared to (30%) the group receiving standard therapy at the end of day 14.⁹ Umifenovir another antiviral has been seen to be effective in small clinical trials when used along with Ribavirin, Interferon-alpha, Oseltamivir, and Methylprednisolone.^{20,21,22} It was used for a patient who had undergone a renal transplant and was immune-compromised. It was seen that decreasing the amount of immunosuppressive drug and increasing methylprednisolone along with Umifenovir showed remarkable results and proved very effective. The patient was discharged on recovery.²¹ Umifenovir needs randomized large scale clinical trials for further assessment. Intravenous Remdesivir was advised to a patient who was previously receiving ibuprofen and acetaminophen for fever, guaifenesin for cough, vancomycin, and cefepime. The patient showed significant improvement after the intravenous

administration of Remdesivir.²⁴ However, there are limited clinical trials of Remdesivir itself and further testing is required as it may be a potential treatment drug as well. Retrospective studies on Oseltamivir have shown that the use of this drug does not bear significant results.²⁶

Traditional Chinese medicine (TCM) has long been used in China for treating influenza and fever. Amidst COVID-19 outbreak traditional Chinese medicine was used in conjunction with western medicines like antivirals, antibiotics, oxygen therapy, interferon, and methylprednisolone.^{4,16,17} Patients receiving a combination of Chinese medicine and Western medicine showed significant improvement. In a clinical trial of 562 patients, both groups showed a lowering of fever but the group receiving a combination of Chinese and Western medicine showed a smoother decrease in body temperature to normal as compared to fluctuating fever in the group receiving only western medicine.²⁸ The group receiving TCM also showed improvement of clinical symptoms like dyspnea, fatigue, cough, and malaise comparatively in shorter duration as compared to the group not receiving TCM. The consumption of corticosteroids was reduced in the group receiving TCM and chest radiographs showed reduced air-space shadowing of lungs. The death rate of severe patients in the group receiving TCM was 15.4% which is less as compared to the group receiving only western medicine (47.4%) [28]. TCM has been seen to show beneficial results when used with LPV/r for COVID-19 [4,17]. Most of the herbal medicines fall into two categories which are drugs used to clear heat and dampness plus detoxification and the drugs that promote blood circulation and relieve blood stasis.³⁰ TCM functions to remove heat and toxicity from the lungs to relieve cough and boost immunity.¹⁷ Moreover, TCM is cheap as compared to modern medicine and is cost-effective. However, it should be kept in mind that in neither of the clinical trials was TCM used alone as it effects slowly and should be used as a palliative treatment along with western medicine to increase efficacy. It should not be used as a single treatment modality.²⁸

Convalescent plasma therapy has been used before during the SARS outbreak.¹⁹ There has been limited work on convalescent plasma therapy for COVID-19 but new trials have started to further assess this option due to remarkable results from studies done previously. The convalescent plasma of the donor contains antibodies against the organism which infected the donor. Antibodies from convalescent

plasma may contribute to decrease viraemia and also to alleviate symptoms. In addition to viral neutralizing antibodies, the acceleration of infected cell clearance by antibodies has also been found in an in-vivo study of the HIV-1 virus.^{9,19} In the case of SARS-COV-2, it was seen that plasma from recovered COVID-19 patient contains antibodies which can reduce the viral load in the host.^{8,19} Moreover, it has shown recovery of patients of COVID-19 who had progressed to ARDS. In a clinical trial of 5 critically ill COVID-19 patients, body temperature returned to normal within 3 days of transfusion. Patients who received convalescent plasma therapy showed negative PCR 12 days after plasma therapy. PaO₂ also returned to normal on day 12. These patients were also receiving other drugs (arbidol, lopinavir/ritonavir, oseltamivir, interferon-alpha, ribavirin, and broad-spectrum antibiotics for other bacterial infections).¹⁹ In another clinical trial of 4 patients, the RT-PCR test for COVID-19 came back negative in 3-22 days and two of the patients developed Anti SARS-CoV-2 IgG approximately 14 days after plasma therapy. These patients were also receiving methylprednisolone, antivirals (lopinavir/ritonavir and interferon-alpha), and mechanical ventilation.⁸ Further trials need to be done on plasma therapy. Till now there have been no serious side effects due to plasma therapy.

Mesenchymal cells have been seen to have the capability of modulating the deranged immune functions in the body by regulating the levels of cytokines in body and C reactive protein.¹³ There has been very little work done on this approach but the results achieved by recent clinical trials are satisfactory. In a clinical trial, 7 patients were injected MSC and 3 patients were included as a control group.¹³ The peripheral lymphocytes of the MSC injected group increased and overstimulated cytokine secreting cells disappeared in 3-6 days. The levels of tumor necrosis factor-alpha decreased and the level of interleukin-10 increased as compared to the control group. The patients in the MSC group were stable and 3 of them were discharged whereas the control group deteriorated comparatively. The HCoV-19 nucleic acid test became negative 13 days after transfusion for all patients of the MSC group. Chest CT showed improvement of pneumonia 9 days after transplantation of MSC with less residual lung opacity on day 15 of transplantation. Thus, MSC IV suspensions prevent a cytokine storm and might be a therapy for severe COVID-19 patients.

Passive immunization has long been used as a treatment and this approach has been studied for

COVID-19 by a series of clinical trials. IVIg is a blood product, obtained from the blood of healthy donors. It contains polyclonal Immunoglobulin G (IgG) that contains a large number of bioactive moieties. Several theories have been proposed to explain its immunomodulatory mechanism including Fc mediated and Fab mediated approaches. Considering its safety and efficacy in improving passive immunity and modulating immune inflammation, high-dose IVIg can be considered a treatment option at the early stage COVID-19 infection.¹⁵ In a clinical trial of 3 patients, IV immunoglobulin was administered at 25grams/day for 5 days.¹⁵ The patients became afebrile in the first 2 days after therapy started and all three of them discharged after a mean stay of 11 days in the hospital. Negative PCR testing of COVID-19 for all three patients came after 5 days of the start of immunoglobulin therapy. Chest CT scans also showed resolution of chest shadows. A high dose of IVIg (0.3-0.5 gram/kg body weight) was used. Another clinical trial was done in which 2 patients received intravenous gammaglobulins.¹¹ The patients also received methylprednisolone, moxifloxacin, arbidol hydrochloride, and oseltamivir for other possible infections by atypical bacteria or influenza virus but all test for these pathogens came back negative. The patient's condition improved by gamma globulin usage and both were discharged after two weeks of treatment. Chest CT scans also showed resorption of previous lesions. Further assessment of this treatment method requires clinical trials.

Limitations

So far, a small number of studies have been conducted on the treatment of COVID-19 patients and most of them were conducted on the Chinese population. More randomized -controlled -trials are needed to evaluate the effectiveness of different treatment strategies at a broader level.

Conclusion

Hydroxychloroquine and azithromycin were found effective in the treatment of COVID-19 patients.^{3,10} LPV/r did not show satisfactory results in most of the COVID-19 patients.^{5,9} TCM was found to be effective when used along with Western medicine but cannot be used as a single modality for treatment.^{4,16,17} Convalescent plasma therapy^{8,19}, Intravenous

Immunoglobulin^{11,15}, and Mesenchymal stem cells transplant¹³ were also found effective. In patients of organ transplant, withdrawal of immunosuppressive drugs, and the use of methylprednisolone along with antivirals had shown significantly good results.²¹ Among all these therapeutic approaches we found convalescent plasma therapy to be most effective.^{8,19}

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