IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 7 Ser.4 (July. 2020), PP 19-25
www.iosrjournals.org

Emerging evidence-basedtherapies in COVID-19

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Abstract:
COVID-19 the ongoing pandemic, a corona virus disease which has affected over 7 million people across 200 countries and territories of the globe in the year 2019-20 which is similar to the previous outbreak of SARS and MERS. This contagious viral infection spreads through contact or droplet infections or through contact with contaminated surfaces; it presents with symptomslike fever, cough, fatigueand shortness of breath. Nucleic acid amplification tests (NAAT), such as RT-PCR. nucleic acid amplification tests (NAAT), such as RT-PCR are used to diagnosecases.Precautions are taken to prevent the spread of the Pandemic like use of masks, PPE, hand washing or use of Sanitizers, self-isolation, maintaining good hygiene etc. As per now there is no specificvaccine/antiviral treatment for itbut many medical agencies havebeen working on it and carrying out trials to check the outcome of the drugs on the patients.This review focuses on the various"emerging evidence-based therapies in covid-19 ".
This article covers therapies and medications currently in use or under trial for the treatment of patients with COVID -19.

Key Words: *COVID 19, RT-PCR, NAAT, SARS,MERS*

Date of Submission: 23-06-2020 Date of Acceptance: 11-07-2020

I. Introduction

COVID-19 or the corona virus disease; the ongoing pandemic of the globe in 2019-2020. The outbreak started in Wuhan, Hubei province, China, in December 2019[1], since then has spread worldwide and has been declared to be a Public Health Emergency of International Concern on 30 January 2020 and recognized it as a pandemic on 11 March 2020, by WHO. [2]The 2019-nCoV belongs to *Betacoronavirus* which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) which lead to the outbreak in 2002 and 2012 respectively.[3]The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia.[4][5][6][7]Older people, and those with underlying medical problems like diabetes, cardiovascular disease, chronic respiratory disease, and cancer are more likely to develop serious illness. Drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, were used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. As of 9th June, in 213 Countries and Territories around the world have reported a total of **7,231,354 confirmed cases** , and a death total of **409,387 deaths**., there is no specific treatment against the new virus COVID -19 Thus various research and trials are done to find effective treatment urgently to combat the pandemic.[8][9]

Joshua Geleris, M.D., Yifei Sun, et. Al Conducted an observational study in New York city and obtained data regarding 1446 consecutive covid-19 hospitalizedpatients, excluding 70 of those who were intubated, died, or discharged within 24 hours. Comparision was then made about outcomes in patients who received hydroxychloroquine with those in patients who did not. 1376 patients,recived Hydroxychloroquinein during a median follow-up of 22.5 days, 811 (58.9%) (600 mg twice on day 1, then 400 mg daily for a median of 5 days). 45.8% of the patients were treated within 24 hours and 85.9% within 48 hours. Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receiveit. A total of 346 patients (25.1%) had a primary end-point event out of which 180 patients were intubated, of whom 66 subsequently died, and 166 died without intubation. By analysis, there was no significant association or either a greatly lowered or an increased risk of the composite end point of intubation or death.[10]

II. Drug Trials

David R. Boulware, M.D., M.P.H., et al conducted a randomized, double-blind, placebo-controlled trial testing hydroxychloroquine as postexposure prophylaxis. They enrolled821 adults who wereexposure to confirmed Covid-19 patient. Within 4 days after exposure, participants were randomly assigned to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days). Overall, 719 of the participants reported a high-risk exposure to a confirmed Covid-19 contact. Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was −2.4 percentage points (95% confidence interval, −7.0 to 2.2; P=0.35). The study concluded that, after high-risk to moderate-risk exposure hydroxychloroquine did not prevent illness.[11]

Philippe GAUTRET, Jean Christophe LAGIEREt. al studied and concluded that Chloroquine and Hydroxychloroquine have been found to be efficient on COV-19, and reported to be efficient in Chinese patients infected by this virus. On evaluation of the role of Hydroxychloroquine on respiratory viral loads. Patients were included in a single arm protocol to receive 600mg of hydroxychloroquine daily and their viral load in nasal swabs was tested daily, azithromycin was added to the treatment depending on the clinical presentation. Presence and absence of virus at Day-6 was considered the end point. 20 cases were treated in this study and showed a significant reduction of the viral carriage at D-6 compared to controls. Azithromycin added to Hydroxychloroquine was significantly more efficient for virus elimination.[12]

Mandeep R Mehra, et. Al dida registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19 between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups and patients who received none of these treatments formed the control group, exclusion being Patients for whom one of the treatments was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir. 96 032 patients with COVID-19, ofwhom 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. 10 698 (11·1%) patients died in hospital. No confirm benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment.Thought, this study was retracted lately and other trials were resumed.[13]

Manli Wang, Ruiyuan Cao, et. Al evaluated and concluded that remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. the antiviral efficiency of five FAD-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro. The effects of these compounds on the cytotoxicity, virus yield and infection rates were measured. Efficacies were evaluated by quantification of viral copy numbers in the cell supernatant viaRT-PCR (qRT-PCR) and confirmed with visualization of virus nucleoprotein expression. Among the seven tested drugs, high concentrations of three nucleoside analogs including ribavirin (half-maximal effective concentration (EC50) = 109.50 μM, half-cytotoxic concentration (CC50) > 400 μM, selectivity index (SI) > 3.65), penciclovir (EC50 = 95.96 μM, CC50 > 400 μM, SI > 4.17) and favipiravir (EC50 = 61.88 μM, CC50 > 400 μM, SI > 6.46) were required to reduce the viral infection However, favipiravir has been shown to be 100% effective in protecting mice.

Nitazoxanide, a commercial antiprotozoal agent with an antiviral potential against a broad range of viruses including human and animal coronaviruses, inhibited the 2019-nCoV at a low-micromolar concentration (EC50 = 2.12 μM; CC50 > 35.53 μM; SI > 16.76). Further in vivo evaluation of this drug against 2019-nCoV infection is recommended. Notably, two compounds remdesivir (EC50 = 0.77 μM; CC50 > 100 μM; SI > 129.87) and chloroquine (EC50 = 1.13 μM; CC50 > 100 μM, SI > 88.50) Our findings reveal that remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro.Since these compounds have been used in human patients with a safety track record and shown to be effective against various ailments. Thus this should be assessed in human patients suffering from the novel coronavirus disease.[3]

John H. Beigel, M.D., Kay M. Tomashek, M.D.., et al.conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in 1063 adults hospitalized. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death,

0.70; 95% CI, 0.47 to 1.04). Thus, it was concluded that Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.[14]

Jason D. Goldman, et. Al, conducted a randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale. 397 patients underwent randomization and began treatment (200 patients for 5 days and 197 for 10 days). The median duration of treatment was 5 days

(interquartile range, 5 to 5) in the 5-day group and 9 days (interquartile range, 5 to 10) in the 10-day group. Patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group (P=0.02). By day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P=0.14). Thus they conclude patients with severe Covid-19 not requiring mechanical ventilation, trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir.[15]

Stephanie A. Kujawski, Karen K Wong, et. Al; studied the Clinical and virologic characteristics of the first 12 patients with covid-19. Among the 12 patients, median age was 53 years (range: 21-68); Patients had mild to moderately severe illness; seven were hospitalized and demonstrated clinical or laboratory signs of worsening during the second week of illness. No patients required mechanical ventilation and all recovered. The clinical or laboratory signs of worsening during the second week of illness. Three were treated with the investigational antiviral remdesivir. [16]

Cai et. Al; concluded that FPV showed better treatment outcomes in COVID-19 patients in terms of their disease progression and viral clearance.A open label, non-randomizedstudy was performed a comprehensive evaluation of the clinical efficacy of treatment for COVID-19 patients aiming to compare the clinical outcomes between patients who treated with FPV and patients treated with LPV/RTV. 56 adult (16-75) laboratory-confirmed patients with COVID-19 were consecutively screened, and eligible patients were included in the FPV arm of the study. Patients who had initially been treated with antiviral therapy with LPV/RTV were included in the control arm of the study.FPV was 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14. LPV/RTV, dose was LPV 400 mg/RTV 100 mg twice daily. Both FPV and LPV/RTV were continued until the viral clearance was confirmed or until 14 d had passed. In addition, all participants received IFN-α1b 60 μg twice daily by aerosol inhalation. Standard care was also availed. Thus, after the enrolled patients finished the therapy,followup was done for 14 d after the treatment began andthe baseline characteristics were compared between the FPV arm and the control.FPV showed better treatment outcomes in COVID-19 patient.[17]

Hidekatsu Yanai et. Al reported that Favipiravir may be a relatively safe and effective drug for COVID-19 at present. Favipiravir being an RNA-dependent RNA polymerase competitive inhibition, the efficacy of viral replication can be largely reduced. Patients were assigned to receive favipiravir(orally) plus interferon-α aerosol inhalation (n = 35), or receive lopinavir/ritonavir which is a fixed-dose protease inhibitor combination used for the treatment of human immunodeficiency virus 1 (HIV-1) [10] plus interferon-α aerosol inhalation (n = 45). A viral clearance time was significantly short in the favipiravir arm than the lopinavir/ritonavir arm by 7 days (median value). Further, multivariable Cox regression showed that favipiravir was independently associated with faster viral clearance. The favipiravir arm also showed significant improvement in chest imaging compared with the lopinavir/ritonavir arm, with an improvement rate of 91.43% versus 62.22% at day 4 after treatment. Total number of adverse reactions in the favipiravir group (n = 4, 11.4%) was significantly smaller than the lopinavir/ritonavir group (n = 25, 55.56%).. The Japanese Association for Infectious Diseases also reported improvement in 90%, 85% and 61%, after 14 days from the start of favipiravir, in mild, moderate and severe COVID-19 cases, respectively.Favipiravir may be a relatively safe and effective drug for COVID-19 at present.[18]

Glenmark Pharmaceuticals has initiated Phase-3 clinical trials in India after showing significant success on the patients in phase 1 and phase 2 , from antiviral tablet Favipiravir .the clinical trial includes, 150 subjects with mild to moderate COVID-19 will be randomised in the study in a 1:1 ratio to Favipiravir with standard supportive care or standalone standard supportive care. Treatmentduration will be maximum of 14 days and the total study duration will be a maximum of 28 days from randomisation Clinical trials have commenced and over 10 leading government & private hospitals in India are being enrolled for the study. [19]

Delang L, Abdelnabi R, Neyts J.et.Al, concluded that the potential of favipiraviras a broad-spectrum antiviral seems promising, but safety and potency issues should be overcome before this drug or similar molecules could be used to treat large patient groups.Favipiravir, also known as T-705, is an antiviral drug approved to treat pandemic influenza virus infections. Favipiravir has already been used off-label to treat patients infected with the Ebola virus and the Lassa virus. Because of the particular set-up of the clinical trials during these outbreaks, clear conclusions on the efficacy of favipiravir could not be made. For several viruses, it was demonstrated that the barrier of resistance development against favipiravir is high. Favipiravir has been

shown to be well tolerated in healthy volunteers and in influenza virus-infected patients. the teratogenic risks of this molecule can not be ignored. Because of its antiviral activity against different RNA viruses and its high barrier for resistance, the potential of favipiravir as a broad-spectrum antiviral seems promising, but safety and potency issues should be overcome before this drug or similar molecules could be used to treat large patient groups.[20]

Bin Cao, M.D., Yeming Wang, M.D., et. Al conducted a randomized, controlled, open-label trial involving 199 hospitalized adult patients with confirmed SARS-CoV-2 infection. 99 were assigned to the lopinavir–ritonavir (400 mg and 100 mg, respectively) (twice a day for 14 days, in addition to standard care, or standard care alone) group, and 100 to the standard-care group. Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, lopinavir–ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). serious adverse events were more common in the standard-care group. no benefit was observed with lopinavir–ritonavir treatment beyond standard care. [21]

C M Chu2,V C C Cheng1, et.Al conducted a study in Forty one patients with SARS followed for 3 weeks were treated with a combination of lopinavir/ritonavir and ribavirin. The clinical progress and virological outcomes were monitored and compared with 111 patients treated with ribavirin only who served as historical controls.In vitro antiviral activity against coronavirus was demonstrated for lopinavir and ribavirin at concentrations of 4 μg/ml and 50 μg/ml, respectively, only at 48 hours. The adverse clinical outcome was significantly lower in the treatment group than in the historical controls (2.4% *v* 28.8%, $p<0.001$) at day 21 after the onset of symptoms. The adverse outcome remained significantly lower in the treatment group than in the controls—both those diagnosed early ($p<0.001$) and those diagnosed later in the course of the epidemic ($p=0.002$)—but there was no significant difference in adverse outcome rates between the two time periods ($p=0.548$). Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level. The apparent favourable clinical response with lopinavir/ritonavir and ribavirin in patients with SARS.[22]

Yang cao , et. Al studied to evaluated the efficacy and safety of ruxolitinib, a Janus-associated kinase (JAK1/2) inhibitor, for COVID-19.They conducted a prospective, multicentre, single-blind, randomized controlled phase II trial involving 43 patients with 20 patients in intervention group and 21 patients in control group were included in the study. Treatment with ruxolitinib plus SoC was not associated with significantly fast clinical improvement in severe patients with COVID-19, although ruxolitinib recipients had a numerically faster clinical improvement. Eighteen (90%) patients from the ruxolitinib group showed CT improvement at D14 compared with 13 (61.9%) patients from the control group ($P = 0.0495$). Ruxolitinib was well tolerated and the Levels of 7 cytokines were significantly decreased in the ruxolitinib group in comparison to the control group.Ruxolitinib recipients had a numerically faster clinical improvement but no statistical difference was seen.Significant chest CT improvement, a faster recovery from lymphopenia and favourable side-effect profile in ruxolitinib group were encouraging and informative to future trials to test efficacy of ruxolitinib in a larger population. [23]

Laa rosee et. Al performed a Retrospective analysis of CIS reduction and clinical outcome was performed. .Out of 105 patients treated , 14 patients with a CIS >/= 10 out of 16 points received Rux over a median of 9 days with a median cumulative dose of 135 mg and a total of 12/14 patients achieved significant reduction of CIS by >/=25% on day 7 with sustained clinical improvement in 11/14 patients without short term red flag warnings of Rux-induced toxicity. Rux treatment for COVID-19 in patients with hyperinflammation is shown to be safe with signals of efficacy in this pilot case series for CRS-intervention to prevent or overcome multiorgan failure. Therefore, a phase II clinical trial should be initiated. [24]

Cavalli, Giulio; et al studied29 patients receiving high-dose intravenous anakinra, non-invasive ventilation, and standard treatment, 16 patients received non-invasive ventilation and standard treatment only and comprised the comparison group for this study. seven patients received low-dose subcutaneous anakinra in addition to non-invasive ventilation and standard treatment; however, anakinra treatment was interrupted after 7 days because of a paucity of effects on serum C-reactive protein and clinical status. At 21 day of treatment with high-dose anakinra was associated with reductions in serum C-reactive protein and progressive improvements in respiratory function in 21 (72%) patients; five (17%) patients were on mechanical ventilation and three (10%) died. In the standard treatment group, eight (50%) of 16 patients showed respiratory improvement at 21 days; one (6%) patient was on mechanical ventilation and seven (44%) died. At 21 days, survival was 90% on the discontinuation of anakinra was not followed by inflammatory relapses. In this retrospective cohort study, Treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients. [25]

Epperly H, Vaughn FL et. Al studied 73 patients (28 studies in adults, 46 studies in children, and one study in adults and children) concerned with acute viral respiratory infections or conditions commonly caused by respiratory viruses, but none specifically addressed COVID-19, SARS, or MERS.Very low certainty evidence on mortality among adults and children. At present there is no evidence of severe adverse events, acute health care utilization, long-term survival, or quality of life in patients with COVID-19, as a result of the use of NSAIDs. [26]

Eric Salazar, et al concluded that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease Patients (n = 25) with severe and/or life-threatening COVID-19 disease were enrolled and transfused with convalescent plasma obtained from donors with confirmed SARS-CoV-2 infection and had recovered. The primary study outcome was safetyand the secondary outcome was clinical status at 14th day of post-transfusion. Clinical improvement was assessed based on a modified WHO 6-point ordinal scale and laboratory parameters. Viral genome sequencing was performed on donor as well as the recipient strains. At day 7 post-transfusion with convalescent plasma, nine patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events were observed. The data indicate that convalescentplasma administrationis a safe treatment option for those with severe COVID-19 disease.[27]

Chenguang Shen, PhD, Zhaoqin Wang, et. Al studied Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS). All 5 patients (age range, 36-65 years) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature was normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and P**ao**2/F**io**2 increased within 12 days. Viral loads also decreased and became negative within 12 days after the transfusionand SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). In this preliminary uncontrolled case administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. [28]

Y O Y Soo et al. Made a Retrospective Comparison of Convalescent Plasma With Continuing High-Dose Methylprednisolone Treatment in SARS Patients. Forty SARS patients with progressive disease after ribavirin – steroid treatment and 1.5 g of pulsed methylprednisolone were given either convalescent plasma (n = 19) or further pulsed methylprednisolone (n = 21) in a retrospective non-randomised study. Good clinical outcome was defined as discharge by day 22 following the onset of symptoms. Convalescent plasma was obtained from recovered patients after informed consent. Patients in the plasma group had a shorter hospital stay (p 0.001) and lower mortality (p 0.049) than the comparator group. No immediate adverse effects were observed following plasma infusion. Thus, convalescent plasma provided better outcomes in various terms. [29]

Emma Morriss, et. Al stated that Dexamethasone an inexpensive drug on the shelf has shown to improve COVID-19 survival by reducing death by up to one third in hospitalised patients with severe respiratory complications of COVID-19.the RECOVERY (Randomised Evaluation of COVid-19 therapy) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone (a steroid treatment). Over 11,500 patients were enrolled.2104 patients in total were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomised to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).Dexamethasone reduced mortality by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support. life of 1/8 patients can be prevented and rest can be managed by Oxygen alone.[30]

Peter Horby, et.al stated that Dexamethasone is the first drug to be shown to improve survival in COVID-19. The survival benefit is clear and large in those patients who are sick enough to require oxygen treatment, so dexamethasone should now become standard of care in these patients. Dexamethasone is inexpensive, and can be used immediately to save lives worldwide.[30]

III. Conclusion

To date, there are no specific vaccines or medicines for COVID-19. Preventive methodshave been used worldwide to decrease the spread of the ongoing pandemic. Supportive care being the standard, while many therapies including chloroquine, hydroxy-chloroquine, antiviral drugs like remdesvir, favipiravir, lopinavir, ritonavir and ribavirin. Ruxolitinib, anakinraanti-inflammatory medications, convalescent plasma, dexamethasone has been proposed to treat COVID-19. Clinical trials to evaluate potential therapies are ongoing.

Although drugs like Dexamethasone, hydroxychloroquineand favipiravir has shown significantly satisfying results and the use ofconvalescent plasma has proved to be very helpful for the treatment of COVID-19.

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