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Systemic Review Article

A Brief Outline of COVID 19 Specific Therapy in Hospitalised Patients In India

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COVID 19 pandemic has a significant impact on global public health and economies. Scientists and researchers all over the world are endeavouring in search of specific drug against COVID19 virus. For a novel emerging virus, specific antiviral drug takes time before its approval for clinical use as RCTs are expensive and time consuming. In Indian perspective, many drugs which are currently under clinical trial are unavailable. Reviewing available published and unpublished papers, we intend to throw light on the drugs that can be used in the interim in India till further evidence come. Pending sufficient evidence remdesivir, favipirvair,tocilizumab,lopinavir-ritonavir with or without ribavirin; hydroxychloroquine or convalescent plasma can be considered.

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The COVID 19 pandemic has a significant impact on global public health and economies.

Coronaviridae family is an important pathogen that primarily affects respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which were epidemic in nature. In December 2019, in Wuhan, Hubei province, China a cluster of patients were admitted with influenza like illness or severe acute respiratory syndrome. The common source of the infection was found to be a seafood and wild wholesale market in Wuhan. The pathogenic virus for the illness was first identified as Novel Corona virus (2019-nCov) and later it was renamed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co V2) after the genetic sequencing.

The first case of the COVID-19 in India was reported on 30 January 2020, in a patient returned from China. As of 5 July, 2020, the Ministry of Health and Family Welfare have confirmed a total of 244,814 active cases, 409,082 recoveries (including 1 migration) and 19268 deaths in the country. At the time of writing, the World Health Organisation (WHO) reported 11,125,245 confirmed cases including 528,204 confirmed deaths globally and 217 countries, areas or territories reporting cases.

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Editor's Comment :

- **Physicians should remain flexible in adopting protocols for treatment based on evolving evidence.**
- **Properly designed RCTs on covid19 specific therapy will possibly change treatment strategy based on strong evidence.**

Such unparallel worldwide effect of the SARS- CoV-2 pandemic has prompted scientific community to explore all possible solutions as there is no evidence based specific antiviral drugs or vaccine against COVID-19 infection till date. Out of many possibilities available, an antiviral drug remains the most crucial option. An effective, safe, and available treatment strategy for the disease is the need of the hour.

Several treatments are being evaluated worldwide. Multiple drugs with in-vitro antiviral activity against SARS-CoV-2 and/or immunomodulatory effects that may have clinical benefit are being tested and their use in COVID 19 patients remain investigational. Some of the drugs are in the verge of getting approval from the respective drug licensing authority but are currently unavailable in India. In Indian scenario the COVID19 specific therapy is likely governed by availability of treatment, established evidence and affordability.

For a novel emerging virus, specific antiviral drug

takes time before its approval for clinical use as RCTs are expensive and time consuming. The drugs which act on similar pathogen and have broad spectrum activity is considered in the interim.

Triple combination therapy (Lopinavir-ritonavir+ ribavirin+interferon beta 1b) :

In a recent multicentre randomised open-label phase 2 trial in patients with COVID-19, triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were found to be more effective and safe to lopinavir–ritonavir alone when introduced early in the disease i.e. within 7 days of the onset of symptoms. The triple combination alleviates symptoms more readily and discontinue viral shedding and facilitates hospital discharge[1]. Interferon beta-1b should not be continued after 7 days of onset of symptoms because of its pro-inflammatory effect. The common side effects were nausea (35%) and diarrhoea (40%), increased alanine aminotransferase (13%) and fever (37%) with no serious adverse event noted. The level of IL 6 was also lower in the triple drug regimen group than the control group.

In India Interferon beta-1b is scarcely available but combination of ritonavir + lopinavir and ribavirin available. So initiation of treatment with double agent lopinavir -ritonavir and ribavirin as early as possible preferably within 7 days of onset of symptoms in the moderate to severe hospitalised patients if there is no contraindication to their use can be considered.

WHO is currently collecting data for SOLIDARITY. "Solidarity" is an international clinical trial to help find an effective treatment for COVID-19, launched by the World Health Organization and partners.Following treatment options were selected in the solidarity trial: Remdesivir; Lopinavir/Ritonavir; Lopinavir/Ritonavir with Interferon beta-1a; and Chloroquine or Hydroxy-chloroquine.WHO removed lopinvar-ritonavir combination from SOLIDARITY trial on the basis of interim reports of the trial and review of the evidence of all trials on the first week of July,2020 as lopinavir-ritonavir combination did not show reduction in mortality in hospitalized patients when compared with standard of care[2].

The RECOVERY trial in UK concluded which they published on 29 June, 2020 that there was no clinical benefit of lopinavir-ritonavir combination in terms of 28 day mortality, risk of progression to mechanical ventilation or duration of hospital stay[3].

Hydroxychloroquine/Chloroquine:

The potential mechanism of action of CQ/HCQ against SARS-CoV-2 is essentially postulation. The virus enter cells by binding to a cell surface receptor called angiotensin-converting enzyme 2 (ACE2). SARS Co-V2 also upregulates the ACE2 expression. Chloroquine may reduce glycosylation of ACE2, and thus prevent SARS Co-V2 from effectively binding to host cells and entering the cell[4]. Savarino et al. hypothesise that CQ might blunt the production of pro-inflammatory cytokines, thereby inhibiting the pathway that subsequently leads to acute respiratory distress syndrome (ARDS). Some viruses enter host cells through endocytosis and is transported within the host cell via endosome, within which the virus can replicate. When the endosome fuses with the acidic intracellular lysosome, this leads to rupture of the endosome with the release of the viral contents. Chloroquine increase the pH of the endosome and interferes with this process[5].

Hydroxychloroquine (HCQ) appears to have more potent antiviral activity than chloroquine(CQ), although clinical evidence of CQ/HCQ on COVID-19 is variable and does not show any clear benefit. In one unpublished randomized trial adding hydroxy-chloroquine to standard treatment in of patients with mild COVID-19 pneumonia without hypoxia resulted in improvement of symptoms and chest imaging findings[6]. In another unpublished randomized trial there was no improvement in terms of discontinuing viral shedding or symptoms on adding hydroxychloroquine to standard treatment by 28 days in hospitalized patients with mild to moderate COVID-19[7].

Published clinical data on CQ/HCQ are limited and have methodologic problems. In an open-label study, use of hydroxychloroquine (200 mg three times per day for 10 days) was associated with higher rate of viral clearance at day 6 compared with no specific treatment (70 versus 12.5 percent)[8]. On other hand in a randomized trial in Shanghai, there was no such difference observed in viral clearance at day 7 with hydroxychloroquine 400mg per day for 5 days compared to standard treatment.Other antiviral agents including interferon were used in both arms, which could have confounding effects[9].

Additionally higher risk of intubation or death (hazard ratio [HR] 2.37) was found in an observational study with use of hydroxychloroquine in patients with COVID19[10] but this had bias as patients who received hydroxychloroquine were older and have comorbidities with introduction of the drug was at later stage. In a multivariate analysis comparing those patients with a propensity score-matched subset who did not receive hydroxychloroquine, there was no association between hydroxychloroquine use and intubation or death

(adjusted HR 1.04).

The RECOVERY trial in UK found no benefit in 28-day mortality or hospital stay or other outcomes in patients receiving hydroxychloroquine in the treatment arm[11].

WHO removed hydroxychloroquine arm from the SOLIDARITY trial on the first week of July, 2020 on the basis of interim reports of the trial as hydroxy chloroquine did not show any clear evidence of reduction in mortality when compared with standard of care. However, the decision is applied only for SOLIDARITY trial[12].

Hydroxychloroquine as prophylaxis :

The basic criteria of a drug that can be used as a pre-exposure prophylaxis is following: 1) Safety profile. 2) Ease of use. 3) Suitable pharmacokinetics and pharmacodynamics. 4) Efficacy and 5) Cost-effectiveness

As HCQ satisfies the above criteria and the selectivity index(Selectivity index is ratio between cytotoxicity and antiviral activity) of HCQ is relatively low, HCQ can be considered in line of prophylaxis till more evidence come where a steady concentration of HCQ can be achieved over a period of time to prevent virus from binding to host cells and also to resist the virus at post entry level. It requires more clinical trials and careful planning to use HCQ as an effective treatment option.

Hydroxychloroquine with azithromycin :

One French study used azithromycin in combination with hydroxychloroquine which was associated with more rapid viral clearance than hydroxychloroquine alone[13], but that study had methodologic concern. Another study failed to show rapid RNA clearance with the combination[14]. We should be aware that both the agents cause prolongation of QTc and hence careful monitoring is needed when this combination is used.

Hydroxychloroquine with Zinc supplementation :

As CQ/HCQ specifically target extracellular zinc to intracellular lysosomes where it interferes with coronavirus replication and zinc deficiency is common in elderly patients and in patients with comorbidities like diabetes, chronic obstructive airway disease, it can be hypothesized that CQ/HCQ with zinc supplementation may be more effective in antiviral activity than CQ/HCQ alone. More studies are required to establish the hypothesis.

Remdesivir :

Remdesivir potently blocks SARS-CoV-2 infection with a high selectivity index. Holshue et al. reported that intravenous remdesivir yielded promising results in the COVID-19 patients[15].

In a study published in Lancet by Yeming Wang *et al*[16], found remdesivir was not associated with clinical benefits of statistical significance. In that trial the patients were with standard care with use of lopinavir-ritonavir, corticosteroid and interferon.

In a summary of subjects receiving remdesivir as compassionate use in USA, nearly 70% of patients had improvement in oxygen requirements and early intubation was seen in on mechanical ventilation. This report had no control group; hence interpretation is difficult. It is early to conclude direct antiviral effect of remdesivir on enhanced viral clearance from respiratory tract, but it suggests promising therapeutic effect[17].

The United States launched Adaptive Covid 19 Treatment Trial (ACTT) to evaluate experimental treatment for COVID-19 under supervision of National Institute of Health. An independent data and safety monitoring board on interim analysis on remdesivira nnounced that remdesivir was better than placebo from the perspective of primary end point ie, time to recovery. Recovery was defined as being well enough for discharge from hospital or returning to normal activity level. In patients treated with remdesivir median time to recovery was 11 days compared to 15 days in placebo group. The study group had 31% faster recovery placebo ($p<0.001$). Moreover preliminary results showed improved mortality rate 8.0% for the drug for the study group versus 11.6% for placebo ($p=0.059$)[18].

The Food and Drug Administration (FDA) approved emergency use of remdesivir in treatment of severe COVID-19 which is defined as SpO2<94% in ambient air, requiring supplemental oxygen, mechanical ventilation or ECMO. The Indian Council of Medical Research (ICMR) also has fast-tracked the roll out of global ''Solidarity'' trial by the World Health Organisation (WHO) which includes remdesivir.

Favipiravir :

Favipiravir (FPV) is a guanine analogue which is approved for influenza since 2014 has shown in vitro inhibition of SARS-CoV-2[19].

In an open label clinical trial by QingxianCai *et al*[20]. FPV arm with interferon alpha showed significantly higher improvement radiologically and also faster viral clearance when compared with liponavir-ritonavir plus interferon alpha. There were fewer adverse events in

the FPV arm compared to control arm.

The possible adverse effect of favipiravir are hyperuricaemia, teratogenicity and QTc prolongation but generally has favourable safety profile. Further, evidence is needed to consider favipiravir as a recommended option against Covid 19.

One Indian Pharmaceutical company has initiated Phase-3 clinical trials in India on antiviral tablet Favipiravir, for which it received approval from India's drug regulator DCGI in late April.

Convalescent plasma :

In an uncontrolled casese ries of 5 SARS C- V2 patients with rapidly progressive acute respiratory distress syndrome (ARDS) with severe pneumonia and high viral load despite antiviral treatment, administration of convalescent plasma containing neutralizing antibody resulted in improvement in the patients' clinical status in terms of defervescence, improved PaO2/FiO2, SOFA score and negative viral load. However, the trial sample size was limited with no controls and the subjects were on other antivirals as well[21].

In another study, 6 COVID-19 subjects with respiratory failure received convalescent plasma at late stage (at a median of 21.5 days after first detection of viral shedding) and all tested negative for SARS-CoV-2 RNA by 3 days after infusionbut 5 patients died eventually thus questioning its effectivity at later stage. It seems thatconvalescent plasma therapy should be initiated as early as possible in hospitalised patients as it does not reduce mortality in critically ill patients but can decrease viral load[22].

The adverse effect of plasma therapy are infection with other pathogen via transfusion, as with any other blood product and hazard of blood product transfusion like transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI). A theoretical concern about the convalescent plasma is potential worsening of immune-mediated tissue damage via antibody-dependent enhancement as well as blunting of endogenous immunity to the virus. Blood product transmission of the SARS-CoV-2 virus has not been documented yet and is very unlikely for a respiratory virus.

Finding appropriate donor with suitable neutralizing antibody is the main challenge in this therapy and also quantitative serologic assays to identify donors with high titre neutralizing antibodies are not yet widely available.

ICMR has given permission for a multicentric phase-2 trial using convalescent plasma on COVID-19 patients with moderate illness, which is currently recruiting.

Tocilizumab :

In severe COVID 19 cytokine storm occurs which is characterized by increased level of interleukin-6 (IL6) and inflammatory markers such as D-dimer and ferritin that lead to ARDS (acute respiratory distress syndrome) and multiorgan failure and causes mortality. Based on this observation blocking of inflammatory pathway to treat COVID19 has been postulated. Tocilizumab in an IL-6 receptor inhibitor which is approved by FDA for the treatment of cytokine release syndrome and other disorders like giant cell arteritis and rheumatoid arthritis.

In an open label study in China 21 patients of COVID 19 with severe oxygen impairment, high CRP and lymphopenia on receiving tocilizumab resulted in improved oxygenation, normalisation of CRP and normalisation of lymphopenia in significant percentage of patients. Absorption of opacity of lung lesion in the CT scan occurred in 90.5% of patients[23].

In a single arm pilot prospective open label study 63 patients with severe COVID 19 disease received tocilizumab and there were improvement in ferritin, CRP, D-dimer and oxygenation(PaO2/FiO2). There was no significant adverse effect[24].

Dexamethasone :

The RECOVERY trial in UK a total of 2104 patients were randomised to receive dexamethasone with a dosing regimen 6mg once daily PO/IV for 10 days and compared with 432 patients on usual care. Dexamethasone reduced death rate in one third of ventilated patients, in one fifth of patients requiring oxygen support and showed no beneficial effect in patients who did not require oxygen support. Based on the results one death can be prevented when treated around eight ventilated patients and around twenty-five patients requiring oxygen support[25]. To determine the subset of patients who will mostly benefit from dexamethasone additional details are needed.

Itolizumab :

Itolizumab is a 'first in class' humanized IgG1 monoclonal antibody which selectively targets CD6, a pan T cell marker involved in co stimulation, adhesion and maturation of T cells. It inhibits the pro-inflammatory cytokine and can be useful option to treat cytokine storm due to COVID 19. Trials in Delhi and Mumbai have been started. Apart from India, the trial on Itolizumab is also ongoing in Cuba.

Conclusion:

With the studies and trials published so far and other preliminary reports several therapeutic options can be used as per physician's discretion though till date, there are no specific evidence based medicines for COVID-19 available. Multiple treatments are under investigation, and will be tested through observational study and RCTs. Pending sufficient evidence, the following drugs and combination of drugs can be considered for treatment for COVID 19 in hospitalised patients in India:

Limitations of the study :

The following are the limitations of this review:

(1) Specific therapy on COVID 19 is evolving continuously. Best choices will keep on changing depending on accrued evidence.

Drugs	Dose and duration	Adverse effect	Remarks
Lopinavir-ritonavir+ Ribavirin	Lopinavir-ritonavir : PO lopinavir 400 mg and ritonavir 100 mg every 12 h for 14 days Ribavirin : PO 400 mg every 12 h for 14 days Interferon beta 1b: 1 mL (8 million international units [IU]) on alternate days subcutaneously for 3 doses twice	Nausea, diarrhoea, increased alanine aminotransferase and fever	The three-drug regimen preferably should be used within 7 days of onset of symptoms. If started within 7 -14 then interferon beta 1 b should be omitted. **This drug has been omitted from SOLIDARITY and RECOVERY trial because lack of beneficial effect.**
Hydroxychl-oroquine	PO 200 mg twice per day for 5 d	Nausea, diarrhoea, prolonged Qtc, bradycardia	Zinc can be combined with HCQ. **HCQ has been omitted from SOLIDARITY and RECOVERY trial because lack of beneficial effect.**
Remdesivir	IV 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia, and increased total bilirubin	Remdesivir is currently available in India. Costly drug. To consider using in severe COVID19
Favipiravir + Interferon alpha	Favipiravir PO Day 1: 1600/ mg twice daily; Days 2–14: 600/ mg twice daily) plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily)	hyperuricaemia, teratogenicity and QTc prolongation	Favipiravir is currently available in India
Convalescent plasma	2 consecutive transfusions of 200 to 250mL of ABO-compatible convalescent plasma (400mL of convalescent plasma in total) on the same day it was obtained from the donor.	Transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI)	To continue other antiviral medications as well
Tocilizumab	IV: 8 mg/kg (maximum: 800mg/dose) as a single dose : may repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve (Genentech 2020)	Showed no significant adverse effect related to tocilizumab in the published trials in COVID 19 patients. Hypersensitivity, hepatic injury, cytopenia, GI perforation, increased risk of infection are the concerns related to adverse effects. Relapse of tuberculosis or activation of latent tuberculosis and malignancy are the concerns who receive tocilizumab for other indications.	Costly drug. Currently under SOLIDARITY and RECOVERY trial
Dexame-thasone	IV/PO: 6mg once daily for 10 days	Adverse report was not reported (including secondary infections)	Not indicated in patients who do not require respiratory support

(2) As the published studies on COVID 19 are mostly observational and the RCTs are confounded with limitations, lack of systematic review or metaanalysis makes review articles open for further discussions.

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Conflict of Interest : None

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