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Compassionate Use of Drugs and India's Status *Viz* Global Status During Pandemic COVID 19

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Abstract:

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to progress, with more than 103 million global cases and more than 2.2 million deaths as of February 2, 2021. While the world awaits the distribution of effective vaccines, a number of pharmacologic agents have been studied for treatment of coronavirus disease 2019 (COVID-19), the syndrome caused by SARS-CoV-2. favipiravir, tocilizumab, Remdesivir, a nucleotide analogue prodrug with in vitro effects against a broad array of RNA viruses,2-4 has received considerable attention. Clinical trials assessing the effectiveness of remdesivir have yielded conflicting results; have not included a sufficient number of patients from groups most affected by COVID-19, such as Black or Latinx individuals; and have not examined the coadministration of remdesivir with other drugs. Within a few months over a thousand clinical trials of potential treatments were launched By 29 April 2020, data from two completed trials and interim data from a third large trial were made available to regulators, in support of the use of remdesivir in patients with COVID-19.

Introduction:

The COVID 19 outbreak has placed unprecedented demands on our health system. Our health facilities and workforce are currently inundated by a plethora of activities related to controlling the pandemic [1]. In doing so, there is a risk that essential health services which communities expect from the health system, would be compromised. It is likely that health seeking may be deferred because of social/physical distancing requirements or community reluctance owing to perceptions that health facilities may be infected [2]. Focusing on COVID 19 related activities, and continuing to provide essential services, is important not only to maintain people's trust in the health system to deliver essential health services1 , but also to minimize an increase in morbidity and mortality from other health conditions. Analyses from the 2014-2015 Ebola outbreak suggests that the increased number of deaths caused by measles, malaria, HIV/AIDS and tuberculosis attributable to health system failures exceeded deaths from Ebola[3] . Particular attention needs to be paid to the delivery of essential health care for specific population sub-groups, while ensuring the safety of health workers. Essential services for all areas include reproductive, maternal, new-born and child health, prevention and management of communicable diseases, treatment for chronic diseases to avoid complications, and addressing emergencies. Non-Covid services such as health promotion activities, IEC campaigns, meetings of the Village Health Sanitation and Nutrition Committees/Mahila Arogya Samitis, community based screening for chronic conditions, other screening programmes, etc. could be deferred and undertaken after lockdown/restrictions are lifted. These services could be considered as desirable [4].

Just to recapitulate, in December 2019, a cluster of cases of pneumonia of unknown origin were reported from the Wuhan city of China, which were identified to be caused by novel coronavirus (CoV), named as the 2019 novel coronavirus (2019-nCoV). The infection was highly contagious with spread by respiratory droplets. China publicly shared the genetic sequence of the COVID-19 on 12th January 2020 [5]. On 13th January 2020, a confirmed case was reported from Thailand. There was a

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rapid spread of the infection in the Wuhan city and around, and by 23rd January 2020, COVID-19 cases had been reported from Hong Kong, Macau and Taiwan. The infection rapidly spread to most of the countries in the next few months. The outbreak was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) in January 2020, and was subsequently designated as a pandemic in March 2020 [6]. In India, the first case of COVID-19 was reported on January 30, 2020 in the state of Kerala. Till 15thJanuary 2021, 92,779,627 confirmed cases of COVID-19 have been reported to the WHO with 1,990,398 deaths. Till mid-January 2021, India has reported 10,527,683 confirmed cases and 151,918 deaths. There has been a second wave of the COVID19 pandemic in the USA and many other countries in Europe and South America in the last few months. COVID-19 pandemic had tremendous adverse effects on the mental health of a wide strata of the population including those detected positive, their caregivers, healthcare workers and the general population due to fear of getting this severe potentially fatal illness [7]. Persons already suffering from mental health problems were further affected due to not being able to access the mental health services. Preventive strategies of the lockdown, which led to closure of various commercial and industrial establishments, as well as entertainment and tourism industry, led to economic shutdown and associated problems. Educational institutions were closed, and healthcare institutions had to divert their services to the COVID-19 specific healthcare facilities [8]. India declared a nationwide lockdown as a preventive strategy for spread of COVID-19 pandemic on 24th March 2020, which was extended in phases to 31st May 2020 and lifted back in a stepwise fashion over the next few months. Many general hospitals were converted partially or completely to COVID care facilities. Our Institute, the All India Institute of Medical Sciences (AIIMS), New Delhi had started holding daily meetings of the Heads of the Departments, chaired by the Director for about a week prior to the lockdown in view of the worsening COVID-19 situation in the country [9].

Materials And Methods:

Study design and participants

The study took place in the mainly Delhi and NCR region of India from March 19, 2020 until June 30, 2020. The Delhi and NCR Region inhabits approximately 710,000 people, constituting an administrative district of India. One of the largest hospitals in Delhi, the Heidelberg Hospital is located in this district with an approximate of 2000 beds including 156 beds with mechanical ventilation [10, 11]. At no point during the pandemic were the capacities of the Hospital and surrounding hospitals exceeded. A national lock-down in India was announced on March 15, 2020 and lasted until April 19th.

Persons of 30-70 age groups who tested positive for SARS-CoV-2 using RT-PCR nasopharyngeal swabs, identified through the registry of the public health authority in the hospital in India between February 7 and June 30, 2020 were screened and asked for consent. At the time of the study, testing was performed based on clinical suspicion, i.e. presence of symptoms or high risk contact. If a participant was not able to give written consent due to death or legal care, we asked first degree relatives or guardians to fill out the survey on behalf of the participant [12]. Consenting participants were contacted after they had completed two weeks of quarantine and were asked to fill out a survey developed by infectious disease clinicians based on findings in the literature (S1 File). Overall data on number of cases and number of cases hospitalized and COVID-related deaths were available from the public health authority. This protocol is for a prospective cohort study investigating maternal and neonatal outcomes in man-women infected with SARS-CoV-2. The purpose of this study is to determine if SARS-CoV-2 infection patient during increases the risk of adverse outcomes. Additionally, this study will characterize the clinical spectrum of COVID-19 in man-women [13].

Data collection

After confirming consent, participants were invited to participate via a phone interview or an electronical or paper-based questionnaire was sent to them to fill out. All data used in this study was collected with the retrospective survey, no other sources were used [14]. The Research Electronic Data Capture (REDCapTM, www.prorect-redcap.org) hosted at the University Hospital Heidelberg was used for data management. REDCapTM is a secure, webbased application, which provides audit trails for tracking data manipulation and export procedures [15].

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Inclusion criteria:

- patient must
- COVID-19 Positive by RTPCR and other official test/kit.
- SPO2 level less than 92% measured by calibrated oxy-meter or another official instrument or appartaus
- Symptomatic; Breathing Problem
- Age should be between 30-70 years
- Gender-Male and Female

Exclusion criteria:

- Severe affected from covid-19

The primary outcome of interest was time to clinical improvement from the start of remdesivir, a composite outcome defined as discharged alive from the hospital without worsening of WHO disease severity score or at least a 2-point decrease in WHO severity score during hospitalization within 28 days or maximum follow-up [16, 17] Failure of clinical improvement was censored at the last day of follow-up or 28 days, whichever came first. Death was also censored at 28 days. The secondary outcome was time to death from the first remdesivir treatment day. Patients who were discharged alive were censored at 28 days to account for death and discharge being competing risks, as previously described [18]. An additional secondary outcome was the time to clinical improvement or to death following administration of both corticosteroids and remdesivir.

Statistical Analysis

A set of demographic characteristics, clinical variables (including admission hospital), and laboratory results were included in the Cox proportional hazards regression models based on clinical interest and knowledge [19]. To account for the nonrandomized assignments of remdesivir and different timing of initial administration, we used time-dependent propensity score matching to create pairs of individuals, with 1 patient treated and the other patient being the most similar patient eligible for treatment at the time of initiation. Beginning from day 0, sequential 1:1 greedy matching without replacement was conducted. Propensity scores were calculated from a time-dependent Cox proportional hazards regression model using the time to first receipt of remdesivir as the outcome, in which the propensity score at a given hospitalization day is the hazard of exposure to remdesivir treatment on that day [20].

To conserve the limited number of diagnostic tests for SARS-CoV-2 RNA by RT-PCR, the entry point of the cohort is SARS-CoV-2 testing or screening of suspected cases or asymptomatic pregnant women, irrespective of hospitalization due to COVID-19. Crossover between groups will be allowed. patient enrolled into the SARS-CoV-2 negative (unexposed) group who seroconvert during the patient will crossover into the SARS-CoV-2 positive (exposed) group [21]. patient who are SARS-CoV-2 negative with unknown serology (unknown) may crossover into the SARS-CoV-2 negative and serology negative (unexposed) group if/when antibody testing becomes available and they test antibody negative.

Exposure status:

Exposed status will consist of patient who have tested positive by RT-PCR for SARS-CoV-2 during. Alternatively, in settings where RTPCR is not available and/or RT-PCR samples cannot be analysed, patient may be enrolled in the exposed group if they have detectable IgG/IgM antibodies. Participants enrolled as unexposed will crossover to the exposed group if there is evidence of seroconversion or positive RT-PCR for SARSCoV-2 after study enrolment. Women who have detectable IgG/IgM antibodies at the onset of the study will be placed in the exposed group only if they have RT-PCR confirmed SARS-CoV-2 infection documented at enrolment [22].

Unexposed status will consist of patient who have had negative testing for SARS-CoV-2 IgG/IgM at time of study entry and at end points: If patient develop acute COVID-19 (as evidenced by positive RT-PCR testing) or demonstrate seroconversion after enrolment, they will crossover to the exposed group. patient with detectable IgG/IgM antibodies at the onset of the study will be excluded if they are RT-PCR negative.

Unknown status will consist of patient who have tested negative or had no testing by RT-PCR for SARS-CoV-2 at time of study entry and at end points.

Result And Discussion:

Consecutive prospective recruitment will occur in a health-care setting where either screening and/or symptomatic testing of SARS-CoV-2 among patient is

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ongoing; typically, this can be a clinic catering for individuals seeking care with COVID-19 suspect symptoms. All patient irrespective of SARS-CoV-2 testing or screening results will be offered to participate until sample size of exposed and unexposed groups is fulfilled.

SARS-CoV-2 positive:

Confirmed by RT-PCR testing. The areas of recruitment may differ based on local resources and SARS-CoV-2 testing protocols but should be done in a manner that limits exposure to research staff as well. Examples of possible recruitment strategies that can be used include: by telephone consent after obtaining status of SARS-CoV-2 testing of patient, at antenatal care appointments/telemedicine visits (routine screening of all patient for COVID-19 [23] can help to facilitate the identification of those who have tested positive), during hospital admission (including labour and childbirth, triage, NICU) or emergency department visit, or in collaboration with COVID-19 testing sites.

SARS-CoV-2 negative:

Recruitment may differ based on local resources and SARSCoV-2 testing protocols. Examples of possible recruitment strategies for this cohort can include by telephone consent after obtaining a negative SARS-CoV-2 RT-PCR test.

Sample size calculation:

The site-specific sample size calculations for this study are informed by estimates of composite adverse neonatal outcome (miscarriage, preterm birth, perinatal death or NICU admission) in patient with SARS-CoV-2 infection compared to patient without SARS-CoV-2 infection in pregnancy. All sample size estimates provided in this section are based on 80% statistical power and type I error at 5% level. Furthermore, this section provides examples of initial sample size estimates on the basis of the proportion expected to have the outcome of interest among the SARS-CoV-2-unexposed (p0) and also the effect size (ES) [24]. The final number of patients to be enrolled in each group (SARS-CoV-2 exposed versus unexposed) will need to be further inflated to account for one or more of the following factors as relevant:

1. Anticipated crossover of patient from the unexposed to exposed group, assumed to be 10% (based on the current estimated prevalence of 10%);

2. Loss to follow-up (LFU) for the primary outcomes involving adverse pregnancy outcomes, assumed to be at 5%;

The primary outcome is a composite outcome of any of the following: (i) miscarriage, (ii) preterm birth >37 weeks, (iii) perinatal death and (iv) NICU admission. The assumption, based on preliminary SARS-CoV-2 data in pregnant women, estimates that the exposed group will have between 11% to 22.5% risk for the composite outcome and the unexposed group will have a 10% to 15% risk for the composite outcome. That is, a relative risk of 1.1 to 1.5 [25] shows examples of sample size estimations for site-specific considerations. The calculations assume equal allocation of 1:1 ratio in terms of group sizes for SARS-CoV-2 exposed to unexposed.

Table 1. Example of sample size estimates for site-specific consideration

Risk ratio	1.1	1.1	1.5	1.5
Prevalence				
group 1 unexposed	0.10	0.105	0.10	0.15
group 2 exposed	0.11	0.1165	0.15	0.225
Unadjusted sample size				
N1	14 747	9255	683	423
N2	14 747	9255	683	423

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Adjusting for LFU				
N1	16 385	10 28 3	758	470
N2	16 385	10 28 3	758	470
Adjusting for seroconversion				
N1	18 205	11 42 5	842	522
N2	14 565	91 41	674	418

Sample size calculation for the pooled data will be based on different cohorts and outcomes to allow for outcome-specific and cohort specific analysis, and the single site-specific sample size will vary with national epidemic contexts and national estimates of adverse composite outcomes.

Data management

WHO will offer support to data management and access to an online data entry platform. The WHO team, within the capacity of research strengthening, will support the development of local data platforms [26]. Implementing partners can opt to manage data on site or through the central WHO repository subject to local circumstances. Further, the WHO/HRP will identify an external Independent Data Monitoring Committee (IDMC) to advise on study conduct and interim analyses of global pooled data.

Summary And Conclusion:

Emergency approvals for the first antiviral to show efficacy were issued in record time considering that information on COVID-19 was released end of December 2019 and the pandemic was officially declared by WHO on 11 March 2020. In the meantime, thousands of trials were initiated, either as master protocols or individual trials, and reviewed by regulatory agencies. The first results of the trials that were of sufficient quality for regulatory purpose were shared and analyzed in full cooperation between regulators, thanks to confidentiality arrangements allowing regulatory authorities (here EMA, FDA, and MHLW/PMDA) to discuss and exchange preliminary applications and assessments.

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