Angelika Batta*, Raj Khirasaria, Vinod Kapoor and Deepansh Varshney

Therapeutic clinical trials to combat COVID-19 pandemic in India: analysis from trial registry

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Abstract

Objectives: With the emergence of Novel corona virus, hunt for finding a preventive and therapeutic treatment options has already begun at a rapid pace with faster clinical development programs. The present study was carried out to give an insight of therapeutic interventional trials registered under clinical trial registry of India (CTRI) for COVID-19 pandemic.

Methods: All trials registered under CTRI were evaluated using keyword “COVID” from its inception till 9th June 2020. Out of which, therapeutic interventional studies were chosen for further analysis. Following information was collected for each trial: type of therapeutic intervention (preventive/therapeutic), treatment given, no. of centers (single center/multicentric), type of institution (government/private), study design (randomized/single-blinded/double-blinded) and sponsors (Government/private). Microsoft Office Excel 2007 was used for tabulation and analysis.

Results: The search yielded total of 205 trials, out of which, 127 (62%) trials were interventional trials. Out of these, 71 (56%) were AYUSH interventions, 36 (28.3%) tested drugs, 9 (7%) tested a nondrug intervention, rest were nutraceuticals and vaccines. About 66 (56%) were therapeutic trials. Majority were single-centered trials, i.e. 87 (73.7%). Trials were government funded in 57 (48.3%) studies. Majority were randomized controlled trials, i.e. 67 (56.8%). AYUSH preparations included AYUSH-64, Arsenic Album, SamshamaniVati etc.

Conclusions: The number of therapeutic interventional clinical trials was fair in India. A clear-cut need exists for an increase in both quantity and quality of clinical trials for COVID-19. Drug repurposing approach in all systems of medicine can facilitate prompt clinical decisions at lower costs than de novo drug development.

Keywords: AYUSH; clinical trials; corona virus; COVID-19; CTRI; India; therapeutic interventions.

Introduction

Corona Virus Disease 2019 (COVID-19) has been the deadlest pandemic of the year 2020 all across the globe and has adversely impacted our lives. This illness is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Commonest symptoms are cough, muscle pain, fever, sore throat, nasal congestion, dyspnea, chest pain or headache. However, its clinical presentation ranges from completely asymptomatic to acute respiratory distress syndrome [1, 2]. Moreover, the virus has a high transmission rate and spreading at very high rates causing a worldwide catastrophe.

Despite rigorous containment and quarantine efforts being implemented globally, the incidence of COVID-19 is on a steep rise, with 10,357,662 laboratory-confirmed cases and 508,055 deaths worldwide, as reported by WHO [3]. Furthermore, nonavailability of any specific drug or vaccine to prevent or treat COVID-19 aids the burden of new cases every day. This worldwide pandemic has compelled researchers and scientists to rework upon different strategies in terms of drugs, treatment and control measures to conquer this deadly infection and prevent any future outbreaks [4]. Many international regulatory authorities are working hard to expedite review for drug development. Meanwhile, interim treatment guidelines for COVID-19 are being updated based on very limited data of already available drugs. Multiple trials are also being done across the world to assess the efficacy of various treatment strategies.
Keeping in mind, the Indian population, and 226,947 active cases and 17,834 deaths till date as per the government report on 2nd July, there is a diehard need to find treatment for this disease [5]. India is pacing up in this race against COVID-19 by encouraging prompt registration of clinical trials for COVID-19 through CTRI. CTRI is a non-profitable organization, asks for mandatory registration of all trials being conducted in India before recruiting the first participant in the trial. Thereby, ensuring quality assurance and Evidence-Based Practice by linking it to the International clinical trial registry of WHO [6].

Clinical trials determine the safety and efficacy of any new therapy being implemented by providing research evidences. Therefore, in response to this global outbreak, we decided to undertake this study, in an attempt to get a complete picture on various treatment modalities being implemented in the clinical trials registered under CTRI. The primary study objectives were to assess the type of interventional studies done, methodological design and novel potential options being considered in the research studies for preventing COVID-19. Further, we also reviewed and compared the safety, efficacy of these therapeutic strategies being studied for prevention or management of high-risk individuals or COVID-19 patients, respectively.

Methodology

All the clinical trials which were registered with CTRI were analyzed using the keyword “COVID” from its inception in March till 9th June 2020. Out of all the search results obtained, the therapeutic interventional studies being conducted in COVID-19 patients were chosen for further analysis. Data were comprehensively analyzed with respect to treatment given, primary end points, geographical distribution, study designs, type of therapeutic intervention preventive or therapeutic and funding.

Following information were collected for each of the clinical trials obtained from the search; type of study (observational/interventional), type of therapeutic intervention (preventive/therapeutic), treatment given, type of treatment given (new treatment or new treatment + standard of care), disease severity (mild/moderate/severe disease), no. of participants, no. of centers (single center/multicentric), duration of study, primary end points, type of the institution undertaking the research (government/private), study design (randomized/single-blinded/double-blinded), sponsors (government/private), phase of clinical trial (Phase 1/2/3/4), and, methodological quality (method of randomization, allocation concealment). Also, various therapy areas were studied in detail.

Statistical analysis

Data were entered in MS Excel sheet 2007 for tabulation and analysis. Descriptive statistics was used for analysis.

Results

The search yielded a total of 205 clinical trials from March 2020 till 9th June 2020 after putting the keyword “COVID”. Out of which, 127 (62%) trials registered under CTRI were interventional, whereas 78 (38%) were observational. Of all the interventional studies, 36 studies (28.3%) tested drugs, 9 (7%) tested a nondrug intervention, 7 (5.6%) were vaccines, 4 (3.1%) were nutraceuticals and the rest, i.e. 71(56%) were Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy (AYUSH) interventions. The distribution of the types of interventions used in different studies is shown in Figure 1. Out of these, therapeutic interventional studies, i.e. 118 trials were considered for further analysis.

In our study, 66 (56%) were therapeutic, 46 (39%) were preventive trials and 6 (5%) were both. Most of the studies were single centered 87 (73.7%) and only 31 (26.3%) were multi-centric trials. All the studies were Indian, 117 (99%) except one which was a part of global study. In India, a maximum number of studies were carried out in Delhi followed by Maharashtra and Gujarat. There were very few studies (<5) being conducted in Rajasthan, Kerala, Haryana, Andhra Pradesh and Orissa. Also, clinical trials were undertaken as government funded studies in 57 (48.3%) studies and 61 (51.7%) were pharmaceutical companies,

Figure 1: Types of interventional studies in COVID-19 patients.
private hospitals and clinics, charitable institutions, NGOs and private medical college sponsored studies. Government sponsors included medical colleges, autonomous research institutes and government funding agencies like ICMR, WHO. Further, we found out that sample size was (<100) in 47 studies, (100–1000) in 46 studies and >1000 in 25 studies.

Similarly, the phase of clinical trials was unclear in 54/118 (45.8%) of the registered clinical trials. Of the remaining clinical trials, 26/118 (20.3%) were Phase 3, 31/118 (26.3%) were Phase 2, 5 were in Phase 4 and 2 in Phase 1. Two trials were in post-marketing surveillance phase.

Comparing the study design, most of the trials were randomized controlled trials 67 (56.8%), 24 (20.3%) were single-arm trials, 15 (12.8%) were non-randomized active controlled trials and 12 (10.1%) were in the category of others. Regarding the method of randomization sequence generation, 18/67 (26.9%) have used computer-generated randomization sequence. Inadequacies in reporting randomization method were observed in the rest (49/67, 73.1%) of which, 4/67 (6%) reported coin toss, lottery, toss of dice and shuffling cards, 3/67(4.5%) reported adaptive randomization, 2/67(3%) reported pre-numbered or coded identical containers and 33/67 (49.3%) each have mentioned as “others” and “not applicable”, when in fact it is applicable and 7/67 (10.4%) have mentioned the type of randomization incorrectly (stratified/permutated) instead of method of generation. Similarly, only 4/67 (6%) randomized clinical trials have reported an appropriate method of concealing the allocation (sequentially numbered opaque sealed envelope); [2/67, 3%] centralized; [46/67, 68.7%] not applicable, [4/67, 6%] case record numbers, [2/67, 3%] pharmacy controlled and [9/67, 13.4%] have mentioned open list of random numbers as the method of concealment.

On analyzing the therapeutic trials further, we found 25 trials assessed new treatment, 39 trials assessed new treatment + standard of care (SOC), whereas eight trials did not define the treatment being given. Considering the disease severity, 17 trials enrolled mild patients, seven moderate, 16 trials included severely diseased patients and 32 trials did not define the patient’s disease status clearly.

Maximum interventional studies included AYUSH preparations followed by pharmacological agents like Hydroxychloroquine (HCQ)/Chloroquine (CQ) alone or in combination with other agents; vaccines and nutraceuticals in COVID-19 patients or high risk individuals. Three vaccine related trials were evaluating the role of BCG vaccine as a potential therapy for prevention or treatment of COVID-19. Some ongoing clinical trials testing AYUSH preparations and drugs for COVID-19 have been highlighted in Table 1, 2 respectively.

The Ayurvedic preparations included Chyavanprash; AYUSH-64; combination of Tinospora cordifolia and Piper longum; Samshamanivi, KhadiradiVati, GhanVati, Murrchhita Tila Taila and Arsenic Album; Ashwagandha; Yashtimadhu; ZingiVir-H etc.

Arsenic Album or Arsenic Album in potentized form of 30 centesimal potency was the most commonly studied homeopathic intervention either alone or in combination with other preparations like Bryonia Alba, Gelsemium, Antimonium, Tartaricum, Crotalus Horridus etc.

The most commonly studied drug was HCQ, followed by Convalescent Plasma therapy; Ivermectin; HCQ in combination with other drugs like Azithromycin, Imatinib, Lopinavir+Rotinavir combination, Remdesivir, Ciclesonide+Ivermectin, Ulinastatin etc. Other drugs studied were Imatinib, Favipiravir, Niclosamide, Melatonin, Losartan, Povidone Iodine, Interferon-gamma, Biologicals like Ivoluzumab, Tocilizumab etc.

Amongst the vaccine trials, BCG vaccine is being studied both as a preventive or therapeutic option. Role Mycobacterium w is also being evaluated in the form of intra-dermal vaccine. Nutraceutical preparations being studied included: Curcumin and adjuvants, Thymoquinone, Virulina etc.

Discussion

Corona Virus Disease 2019 (COVID-19) had its origin in Wuhan, China in December 2019 and has spread to many nations. Moreover, WHO declared it a pandemic on 12 March 2020. Since the outbreak of this mysterious virus is rapidly spreading all over the world with thousands reported to have contracted the disease, some of whom died, the search for various treatment options have taken highest priority. The present study is an audit of various therapeutic interventional trials registered under CTRI from its inception in the month of March till 9th June 2020 for COVID-19.

Our study reflects that a majority of the registered trials were interventional studies and some of them being observational; an emboldening finding. Majority of the clinical trials were single-centered, randomized-controlled trials and were therapeutic in nature. Maximum number of trials analyzed new treatment in addition to the SOC. Guidelines mentioned in the Clinical Management Protocol: COVID-19 given by government of India was considered as SOC for comparison [7].

Considerable number of trials had an unclear phase, inadequately reported the method of randomization, allocation concealment and did not define the patient’s disease
Table 1: Some ongoing clinical trials in India using AYUSH preparations for COVID-19.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Trial name (scientific name)</th>
<th>Intervention</th>
<th>Study design</th>
<th>No of participants</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Site</th>
<th>Sponsor</th>
<th>Preventive (P)/Therapeutic (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Evaluation of the immunostimulatory(Shareera Bala) potential of Ayurveda management protocol in Cohort of Delhi Police – an Exploratory clinical study</td>
<td>1. Tab SamshamaniVati 250 mg 2 bid after food with water. 2. Application of Anu taila 2 drops each nostril once a day after bath in the morning 3. Gargle with warm water mixed with rock salt and turmeric 4. Ayush preventive guidelines for COVID 19 with Yoga and Pranayama - for 8 week</td>
<td>Randomized, Parallel group trial</td>
<td>50000</td>
<td>3 months</td>
<td>Improvement in Bala of an individual Immunostimulation leading to nondevelopment of symptoms of COVID-19 in risk population exposed to infected individuals. (Bala will be assessed by using specialized proforma including dasvidha par- eeksha and other questionnaires which will reveal the physical and mental health of an individual)</td>
<td>All India institute of Ayurveda, Delhi</td>
<td>Government P</td>
<td></td>
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<td>2</td>
<td>Effect of an Ayurvedic formulation as add-on to standard of care in COVID-19 positive patients in a tertiary hospital</td>
<td>90–100 ml of kashaya of <em>Tinospora cordifolia</em> stem added with 2g of finely powdered dried Piperlongum fruit, once in the morning before breakfast and once in the evening Before dinner as add on therapy in addition to standard of care medicine</td>
<td>Nonrandomized, active controlled trial</td>
<td>60</td>
<td>1 year</td>
<td>Percentage of patients progressing to serious/critical stage of disease Progress of disease as per clinical severity score (COCSS) No. of days of treatment, hospitalization, type of care and site of treatment at hospital, oxygen support requirement, days of ventilation Required, period of convalescence and return to normal life activity No. of days taken to test negative for COVID, total days to discharge from hospital Profiling according to tridosha Defining the disease according to Ayurveda</td>
<td>Medanta institute of Education and research, Gurgaon, Haryana</td>
<td>Government T</td>
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<td>S. No</td>
<td>Trial name (scientific name)</td>
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<td>3</td>
<td>A single blind, single arm clinical trial to ascertain the effect of Homoeopathic medicines in arresting the pathogenesis of disease in asymptomatic corona virus and suspected corona virus Patients</td>
<td>100 ml water with 1 drop of indicated Homoeopathic medicine (Arsenic Album, Bryonia Alba, Gelsemium, Antimonium Tartaricum, CrotalusHorrudis) in 30/200/1 M potency every 2 hourly. Oral route of Administration. Duration of therapy will be 30 days.</td>
<td>Single arm trial</td>
<td>100</td>
<td>2 months</td>
<td>Primary endpoint of this trial will be measured in terms of clinically recovered case (Covid-19 negative) or appearance of symptoms where conventional treatment starts.</td>
<td>Naiminath homoeopathic medical college, Hospital and research centre, Agra</td>
<td>Private</td>
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<td>4</td>
<td>Evaluation of efficacy and safety of Ayurveda intervention (Ayush-64) add-on therapy for patients with COVID-19 infection (Stage I)-A randomized controlled clinical trial</td>
<td>AYUSH 64: 2 Tablets (500 mg each) thrice daily with water after meal for 1 month.</td>
<td>Randomized, Parallel group, active controlled trial</td>
<td>60</td>
<td>1 year</td>
<td>Clinical cure rate: Time to negative conversion of severe acute respiratory syndrome corona-virus 2.</td>
<td>Government medical college, Nagpur</td>
<td>Government</td>
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<tr>
<td>5</td>
<td>Impact of Ayurvedic interventions in prevention of COVID-19 infection in containment areas of Delhi-A community based study</td>
<td>1. SamshamaniVati 500 mg two times before meal with water for 1 month 2. Sudarshna Ghanavati 500 mg two times before meal with water for one month. 3. Ashwagandha 500 mg two times before meal with water for 1-month total duration of therapy is 1 month</td>
<td>Single arm trial</td>
<td>1324</td>
<td>3 months</td>
<td>Incidence of COVID 19 positive cases (as confirmed by hospital by standard investigation (real-time polymerase Chain reaction test) among Ayurveda users</td>
<td>3 containment zone of COVID 19 atDelhi (Dinpur, inderpuri,nangloi)</td>
<td>Government</td>
<td>P</td>
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<td>6</td>
<td>Evaluating the efficacy of homeopathic combinations for prophylaxis and treatment of viral fevers including COVID19</td>
<td>Use of homeopathic medicines in Prophylaxis/Treatment of viral fevers/COVID19 Combination of Aconite 30, Arsenic album 30, Allium Cepa 30,</td>
<td>Nonrandomized, active controlled trial</td>
<td>10000</td>
<td>2 months</td>
<td>How many people get viral fever/COVID19 after taking the medicine</td>
<td>Cancer aid Society, Lucknow</td>
<td>Private</td>
<td>P</td>
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<td>7</td>
<td>Effectiveness of Arsenicum album 30c in prevention of Covid-19 in individuals Residing in Hot Spots of Red Zones—A multicentric, Randomized, Cluster Level, controlled trial</td>
<td>Influenzum 30, Gelsmium 30, Eupatorium 30, Echinacia 0, Thuja 0 The Arsenicum album 30C will be given to the high risk contact of COVID 19 cases and residing in hotspots of containment zone. The four pills of medicine will be given orally Twice daily for seven days.</td>
<td>Cluster randomized trial</td>
<td>33000</td>
<td>2 months</td>
<td>Confirmation of diagnosis for COVID-19 infection based on RT-PCR/end of quarantine period as per standard protocol. Every third day till 21st day.</td>
<td>11 sites Hot spots in various states</td>
<td>Government P</td>
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<td>8</td>
<td>Ashwagandha for the prophylaxis against SARS-CoV-2 infection: A randomized hydroxychloroquine controlled clinical trial in health care Providers</td>
<td>Ashwagandha (Withania Somnifera) has immunomodulant and immune enhancing activity. It is antioxidant And promotes health 250 mg, 2 tablets twice a day for 12 weeks</td>
<td>Randomized, Parallel group, active controlled trial</td>
<td>400</td>
<td>3 months</td>
<td>(i)Proportion of SARS-CoV-2 infection free participants on completion of study (ii)Proportion of participants contracting COVID-19 during the study period</td>
<td>RRAP Central Ayurveda research Institute for Cancer CCRAS, Mumbai</td>
<td>Government P</td>
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<td>9</td>
<td>A prospective nonrandomized open labeled controlled interventional study on the effect of Chyavanprash Lehyam as a prophylactic measure among high risk population (health care Workers/Containment Zone population) exposed to COVID-19</td>
<td>CHYAVANPRASH LEHYAM-12 g X two times a day (Morning on empty stomach and night before going to bed) for one month</td>
<td>Nonrandomized, active controlled trial</td>
<td>5000</td>
<td>3 months</td>
<td>Comparative assessment of occurrence of COVID-19 infection in healthy volunteers in community having at least 1 confirmed case already identified with control arm of standard Prophylactic Care</td>
<td>National institute of Indian medical Heritage (CCRAS), Hyderabad</td>
<td>Government P</td>
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<td>10</td>
<td>A prospective nonrandomized open labeled controlled interventional study on the effect of Guduchi (Tinospora cordifolia) as a prophylactic measure among high-risk population (health care Workers/Containment Zone population) exposed to COVID-19</td>
<td>GUDUCHI CAPSULE-250 mg X 2 capsules b.d, for one month</td>
<td>Nonrandomized, active controlled trial</td>
<td>5000</td>
<td>3 months</td>
<td>Comparative assessment of occurrence of COVID-19 infection in healthy volunteers in community having at least 1 confirmed case already identified with control arm of standard Prophylactic Care</td>
<td>National institute of Indian medical Heritage (CCRAS), Hyderabad</td>
<td>Government P</td>
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<tr>
<td>1</td>
<td>Hydroxy chloroquine, in open labeled, randomized intervention for prevention of new infection and adverse outcomes following COVID-19 infection - A Tertiary Hospital based study</td>
<td>Hydroxychloroquine 300 mg daily×seven days followed by 300 mg weekly×seven weeks</td>
<td>Randomized, Parallel group, active controlled trial</td>
<td>500</td>
<td>3 months</td>
<td>Percentage of patients who had clinical improvement on 7 and 14 days</td>
<td>Aster Malabar Institute of medical Sciences, Kozhikode, Kerala</td>
<td>Private</td>
<td>P</td>
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<td>2</td>
<td>A randomized controlled trial of hydroxychloroquine prophylaxis for Healthcare workers exposed to COVID-19</td>
<td>800 mg of hydroxychloroquine on the day of enrolment and 400 mg once a week after that for a total of 12 weeks Along with standard care Personal protective equipment</td>
<td>Randomized, Parallel group trial</td>
<td>10990</td>
<td>one year</td>
<td>Proportion of laboratory confirmed symptomatic COVID-19 cases between the groups at the end of six months</td>
<td>Apollo Hospitals, Tamil Nadu St. John's medical college &amp; Hospital, Karnataka The George institute for global Health, India, Delhi</td>
<td>Private</td>
<td>P</td>
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<td>3</td>
<td>An international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care</td>
<td>Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days) Lopinavir with ritonavir (orally twice daily for 14 days) plus interferon (daily injection for six days). Lopinavir with ritonavir (orally twice daily for 14 days) Remdesivir (daily infusion for 10 days)</td>
<td>Randomized, Parallel group, Multiple arm trial</td>
<td>7000 total 1500-in India</td>
<td>1 year</td>
<td>All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study</td>
<td>All India institute of medical Sciences, Jodhpur, Rajasthan Apollo hospitals Enterprises Limited, Tamil Nadu BJ medical college and Civil Hospital Ahmedabad, Gujarat Chirayu medical college and Hospital, Madhya Pradesh GMERS medical college &amp; hospital - Gotri, Gujarat Lead institute for this trial is ICMRNational AIDS research Institute, Maharashtra Sardar Vallabhai Patel (SVP) Hospital, Department of medicine, Gujarat</td>
<td>Government</td>
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<td>4</td>
<td>A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 Associated</td>
<td>Convalescent plasma, two doses of 200 mL each, from recovered COVID-19 patient.</td>
<td>Randomized, Parallel group, active controlled trial</td>
<td>452</td>
<td>6 months</td>
<td>The primary outcome is a composite measure of the avoidance of –1. Progression to severe ARDS</td>
<td>39 sites Government medical college Surat, Gujarat Karnataka Institute of Medical Sciences Hubli,</td>
<td>Government</td>
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<td>5</td>
<td>Complications in moderate disease.</td>
<td>Ivermectin doses are as follows (based on bodyweight): 15–24 kg: 3 mg PO once 25–35 kg: 6 mg PO once 36–50 kg: 9 mg PO once 51–65 kg: 12 mg PO once 66–79 kg: 15 mg PO once 80 and 15 kg: 200 µg/kg PO once</td>
<td>Randomized, Parallel group, active controlled trial</td>
<td>50</td>
<td>1 year</td>
<td>To study if Ivermectin can reduce the viral load in patients with hematological illnesses who are admitted with COVID 19 infection</td>
<td>Karnataka</td>
<td>Private</td>
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<tr>
<td>6</td>
<td>A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 Associated Complications</td>
<td>200 ml of ABO compatible plasma transfusion will be done to the subject randomized for the therapy</td>
<td>Randomized, Parallel group trial</td>
<td>100</td>
<td>1 year</td>
<td>Avoidance of –1. Progression to severe ARDS (P/F ratio 100) and 2. All-cause mortality at 28 days</td>
<td>Max Super Speciality hospital, Saket</td>
<td>Private</td>
<td>T</td>
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<tr>
<td>7</td>
<td>Randomized controlled trial to compare efficacy of hydroxychloroquine alone and in combination with azithromycin in treatment of COVID-19</td>
<td>HCQ 400 mg BD AZT 500 mg OD D1 HCQ 400 mg OD AZT 250 mg OD D2 – D5 HCQ 600 mg BD D1 HCQ 300 mg BD D2 – D5</td>
<td>Randomized, Parallel group trial</td>
<td>300</td>
<td>1 year</td>
<td>COVID Ordinal Outcomes Scale is defined as: 1. Death 2. Hospitalized on invasive mechanical ventilation 3. Unconsciousness 4. Severe respiratory distress</td>
<td>6 sites</td>
<td>Government</td>
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(Batt et al.: CTRI, COVID-19, therapeutic interventional trials)
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<tbody>
<tr>
<td>8</td>
<td>Itolizumab1.6 mg/kg dose iv infusion, if well tolerated and improvement occurs then continue with 1.6 mg/kg dose every two weeks or 0.8 mg/kg weekly Regimen</td>
<td>Randomized, Parallel group, active controlled trial</td>
<td>30</td>
<td>3 months</td>
<td>One-month mortality rate between the two arms</td>
<td>MAMC medical college and LokNayak Jai Prakash Narayan Hospital, Delhi</td>
<td>Narayana Health, Karnataka</td>
<td>Seth GS medical college and KEM Hospital, Maharashtra</td>
<td>Private T</td>
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HCQ 400 mg BD on D1 and 400 mg OD on D2 – 5

ventilation or extracorporeal mechanical ventilation (ECMO)
3. Hospitalized on noninvasive ventilation or high-flow nasal cannula oxygen therapy
4. Hospitalized on supplemental oxygen
5. Hospitalized not on supplemental oxygen
6. Not hospitalized with limitation of activity (due to continued symptoms)
7. Not hospitalized without limitation in activity (no symptoms)
status clearly. Approximately equal no. of trials were being sponsored by the government and pharmaceutical companies which is dissimilar to a study done by Karekar et al. on pregnant women [8]. This might be due to the stringent regulations as well as incentives for companies to conduct studies on COVID-19 patients.

While comparing the primary end points mentioned in the CTRI registered trials, it was astonishing to know that most of the trials were in concordance with the various examples of the appropriate efficacy endpoints specified in the guidance document issued by the USFDA [9]. However, there were only two categories demarcated in the guidance document; one for out-patient treatment trial and second trial for severe/critically ill patients.

Majority of the trials were AYUSH preparations. Ministry of AYUSH and Council of Scientific & Industrial Research (CSIR) have initiated an ambitious and comprehensive research program to evaluate the therapeutic usefulness of Ayurvedic formulations in the medical management of COVID-19. Several Rasayana drugs in Ayurveda are well known to enhance the host immunity which is pivotal to fight any infection. Amongst them AYUSH-64, a poly-herbal drug has been studied in many trials. Ingredients of AYUSH-64 have shown anti-inflammatory and immunomodulatory activities and has been successfully used for management of Influenza like illness [10]. SamshamaniVati is well documented for anti-viral, anti-inflammatory and immunomodulatory potential (Rasayana) and in particular respiratory infections [11]. Yashtimadhu (Mulari) is a popular household remedy from Ayurveda pharmacopeia to treat common cold, flu-like illness and sore throat. It is well known to have anti-inflammatory and immunomodulatory properties and is being studied for COVID-19 [12, 13]. Chyavanprash has also being tried in some trials as it boosts host’s immunity [14, 15] Similarly, Arsenic album which is found to be effective in flu-like illnesses is also one the most studied preparation amongst the homeopathic trials [16].

Out of all the studies, 28.3% were pharmacological interventions. Out of these, majority of the trials included HCQ/CQ alone or in combination with other drugs. Being an effective anti-malarial and an anti-inflammatory drug, it has been demonstrated to have broad-spectrum anti-viral activities by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV in cell culture and in animal studies [17, 18]. In one open labeled nonrandomized French study, CQ/HCQ has shown a significant reduction in viral load compared to the control group [19]. A number of recent publications have favored the use of CQ and its related compound HCQ against COVID-19 [20–23].

Moreover, USFDA and ICMR have recommended HCQ amongst exposed health care workers [24, 25]. Accordingly, repurposing of old and approved drugs such as chloroquine, HCQ, azithromycin, angiotensin-receptor inhibitors such as sartans, or statins such as simvastatin are being considered to be useful for this disease [26]. WHO study includes remdesivir, hydroxychloroquine, lopinavir plus ritonavir, and interferon-beta. Some are given as daily pills, and some as daily injections [27].

Many trials are being carried out on use of Convalescent Plasma therapy. USFDA has recently approved Convalescent Plasma from patients recovered from COVID 19 for the treatment of severe or life threatening COVID-19 infections [28]. In a small case series, five critically ill COVID-19 patients with ARDS were treated with convalescent plasma containing neutralizing antibodies. Infusion of plasma was followed by improvement in clinical status in all five patients, with no deaths and the study reported that three patients were discharged, whilst two continued to be stable on mechanical ventilation [29]. Contrary to this, a study by Ling Li et al. shows no significant clinical improvement when convalescent plasma therapy was added to standard treatment in patients with severe or life-threatening COVID-19 [30].

Ivermectin has shown anti-viral activity in vitro against SARS-CoV-2 and is being investigated for its possible benefit in humans [31]. Our study also includes few trials which aim to confirm the antiviral effectiveness of Ivermectin on coronavirus and thereby establish its potential use in the combating to the COVID 19 pandemics.

Considering the vaccine trials, BCG vaccine is being studied both as a preventive or therapeutic option to fight this disease. BCG vaccination has shown to correlate with reduced COVID-19 case fatality rates [32]. Also, Mycobacterium w due to its immuno-modulatory properties is also being studied for COVID-19 [33].

Amongst the nutraceuticals, curcumin is being studied as a useful preventive option due to its anti-viral, immunity-boosting properties and claims to reduce morbidity and mortality in this outbreak [34, 35].

At present, various diagnostic kits to test for COVID-19 are available, and repurposing therapeutics has shown to be clinically effective. As the global demand for therapeutics and vaccines continues to rise, it is essential to rapidly develop various algorithms to successfully identify and contain the virus [4].

Limitations

Enrollment of trials for COVID-19 under CTRI is an ongoing process due to which we were unable to analyze other
clinical trials which have been registered after 9th June. Also, comparison of Indian trials with western countries ongoing trials in terms of therapeutic interventions could not be studied.

Conclusion
This study has significant scope to add to the existing repertoire of understanding about the management of COVID-19. It will help doctors and other health care professionals in identifying various therapeutic options being tried for COVID-19 in India. Drug repurposing or repositioning approach in all systems of medicine thus can facilitate prompt clinical decisions at lower costs than de novo drug development. Moreover, overcome the time limitation of research and development needed to design a therapeutic drug to combat the pathogen. Furthermore, researchers and trial sponsors should aim at publication of the research findings so that it is made publically available for use.

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References