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 non-drug 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, Samshamani Vati 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 deadliest 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 adds 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.

*Corresponding author: Dr. Angelika Batta, Assistant Professor, Department of Pharmacology, Faculty of Medical & Health Sciences, SGT Medical College, Hospital and Research Institute, SGT University, Gurugram, Haryana, India, Mobile: 9958799366, E-mail: angelikabatta87@gmail.com

Raj Khirasaria, Medical Affairs, Sanofi Genzyme India, Saket District Center, Saket, New Delhi 110017, India

Vinod Kapoor, Department of Pharmacology, Faculty of Medical & Health Sciences, SGT Medical College, Hospital and Research Institute, SGT University, Gurugram, Haryana, India

Deepansh Varshney, Faculty of Medical & Health Sciences, SGT Medical College, Hospital and Research Institute, SGT University, Gurugram, Haryana, India

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, 24/118 (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*; SamshamaniVati, 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 Itolizumab, 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 CTIR 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.

S. No:	Trial name (scientific name)	Intervention	Study design	No of participants	Duration	Primary endpoint	Site	Sponsor	Preventive (P)/Therapeutic (T)
1	Evaluation of the immunostimulatory(Shareera Bala) potential of Ayurveda management protocol in Cohort of Delhi Police – an Exploratory clinical study	1. Tab SamshamaniVati 250 mg 2 bid after food with water. 2. Application of Anu taila 2 drops each nostrils 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	Randomized, Parallel group trial	50000	3 months	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 parieksha and other questionnaires which will reveal the physical and mental health of an individual)	All India institute of Ayurveda, Delhi	Government	P
2	Effect of an Ayurvedic formulation as add-on to standard of care in COVID-19 positive patients in a tertiary hospital	90–100 ml of kashaya of <i>Tinospora cordifolia</i> stem added with 2g s 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	Nonrandomized, active controlled trial	60	1 year	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 tri-dosha Defining the disease according to Ayurveda	Medanta institute of Education and research, Gurgaon, Haryana	Government	T

Table 1: (continued)

S. No:	Trial name (scientific name)	Intervention	Study design	No of participants	Duration	Primary endpoint	Site	Sponsor	Preventive (P)/Therapeutic (T)
3	A single blind, single arm clinical trial to ascertain the effect of Homeopathic medicines in arresting the pathogenesis of disease in asymptomatic corona virus and suspected corona virus Patients	100 ml water with 1 drop of indicated Homeopathic medicine (Arsenic Album, Bryonia Alba, Gelsemium, Antimonium Tartaricum, Crota-lus-H-orruidus) in 30/200/1 M potency every 2 hourly. Oral route of Administration. Duration of therapy will be 30 days	Single arm trial	100	2 months	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	Naiminath homoeopathic medical college, Hospital and research centre, Agra	Private	T
4	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	AYUSH 64; 2 Tablets (500 mg each) thrice daily with water after meal for 1 month	Randomized, Parallel group, active controlled trial	60	1 year	Clinical cure rate: Time to negative conversion of severe acute respiratory syndrome corona-virus 2.	Government medical college, Nagpur	Government	T
5	Impact of Ayurvedic interventions in prevention of COVID-19 infection in containment areas of Delhi- A community based study	1. Samshamani Vati 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	Single arm trial	1324	3 months	Incidence of COVID 19 positive cases (as confirmed by hospital by standard investigation (real-time polymerase Chain reaction test) among Ayurveda users	3 containment zone of COVID 19 at Delhi (Dinpur, Inderpuri, nangloi)	Government	P
6	Evaluating the efficacy of homeopathic combinations for prophylaxis and treatment of viral fevers including COVID19	Use of homeopathic medicines in Prophylaxis/Treatment of viral Fevers/COVID19 Combination of Aconite 30, Arsenic album 30, Allium Cepa 30,	Nonrandomized, active controlled trial	10000	2 months	How many people get viral fever/COVID19 after taking the medicine	Cancer aid Society, Lucknow	Private	P

Table 1: (continued)

S. No:	Trial name (scientific name)	Intervention	Study design	No of participants	Duration	Primary endpoint	Site	Sponsor	Preventive (P)/Therapeutic (T)
7	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	Influenzum 30, Gels-mium 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.	Cluster randomized trial	33000	2 months	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.	11 sites Hot spots in various states	Government	P
8	Ashwagandha for the prophylaxis against SARS-CoV-2 infection: A randomized hydroxychloroquine controlled clinical trial in health care Providers	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	Randomized, Parallel group, active controlled trial	400	3 months	(i) Proportion of SARS-CoV-2 infection free participants on completion of study (ii) Proportion of participants contracting COVID-19 during the study period	RRAP Central Ayurveda research Institute for Cancer CCRAS, Mumbai	Government	P
9	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	CHYAVANPRASH LEHYAM-12 g X two times a day (Morning on empty stomach and night before going to bed) for one month	Nonrandomized, active controlled trial	5000	3 months	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	National Institute of Indian medical Heritage (CCRAS), Hyderabad	Government	P
10	A prospective nonrandomized open labeled controlled interventional study on the effect of Guduchi (<i>Tinospora cordifolia</i>) as a prophylactic measure among high-risk population (health care Workers/Containment Zone population) exposed to COVID-19	GUDUCHI CAPSULE-250 mg X 2 capsules b.d, for one month	Nonrandomized, active controlled trial	5000	3 months	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	National Institute of Indian medical Heritage (CCRAS), Hyderabad	Government	P

Table 2: Some ongoing clinical trials in India using Drugs for COVID-19.

S. No:	Trial name (scientific name)	Intervention	Study design	No of participants	Duration	Primary endpoint	Site	Sponsor	Preventive (P)/Therapeutic (T)
1	Hydroxy chloroquine, in open labeled, randomized intervention for prevention of new infection and adverse outcomes following COVID-19 infection -A Tertiary Hospital based study	Hydroxychloroquine 300 mg daily×seven days followed by 300 mg weekly×seven weeks	Randomized, Parallel group, active controlled trial	500	3 months	Percentage of patients who had clinical improvement on 7 and 14 days	Aster Malabar Institute of medical Sciences, Kozhikode, Kerala	Private	P
2	A randomized controlled trial of hydroxychloroquine prophylaxis for Healthcare workers exposed to COVID-19	800 mg of hydroxy-chloroquine 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	Randomized, Parallel group trial	10990	one year	Proportion of laboratory confirmed symptomatic COVID-19 cases between the groups at the end of six months	3 sites Apollo Hospitals, Tamil Nadu St. John's medical college & Hospital, Karnataka The George institute for global Health, India, Delhi	Private	P
3	An international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care	Chloroquine or hydroxy-chloroquine (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)	Randomized, Parallel group, Multiple arm trial	7000 total 1500-in India	1 year	All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study	7 sites 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 & hospital - Gotri, Gujarat Lead institute for this trial is ICMR National AIDS research Institute, Maharashtra Sardar Vallabhai Patel (SVP) Hospital, Department of medicine, Gujarat	Government	T
4	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 Associated	Convalescent plasma, two doses of 200 mL each, from recovered COVID-19 patient.	Randomized, Parallel group, active controlled trial	452	6 months	The primary outcome is a composite measure of the avoidance of -1. Progression to severe ARDS	39 sites Government medical college Surat, Gujarat Karnataka Institute of Medical Sciences Hubli,	Government	T

Table 2: (continued)

S. No:	Trial name (scientific name)	Intervention	Study design	No of participants	Duration	Primary endpoint	Site	Sponsor	Preventive (P)/Therapeutic (T)
	Complications in moderate disease.					(P/F ratio 100) or 2. All-cause mortality at 28 days	Karnataka Madras medical college, Tamil Nadu Madurai Medical College, Tamil Nadu Mahatma Gandhi Medical College and Hospital Jaipur, Rajasthan Secunderabad, Telangana Government Institute of Medical Sciences Greater Noida, Uttar Pradesh Government Medical College Bhavnagar, Gujarat Govern- ment Medical College Nagpur, Maharashtra Dept. of Hematology, Chris- tian Medical College Vellore		
5	A phase IIB open label ran- domized controlled trial to evaluate the efficacy and safety of Ivermectin in reducing viral loads in pa- tients with hematological disorders who are admitted with COVID 19 infection	Ivermectin doses are as fol- lows (based on body weight) 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 ug/kg PO once	Randomized, Parallel group, active controlled trial	50	1 year	To study if Ivermectin can reduce the viral load in patients with hematological ill- nesses who are admitted with COVID 19 infection		Private	T
6	A phase II, open label, ran- domized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 Associated Complications	200 ml of ABO compatible plasma transfusion will be done to the subject ran- domized for the therapy	Randomized, Parallel group trial	100	1 year	Avoidance of –1. Pro- gression to severe ARDS (P/F ratio 100) and 2. All-cause mor- tality at 28 days	Max Super Speciality hospi- tal, Saket	Private	T
7	Randomized controlled trial to compare efficacy of hydroxychloroquine alone and in combination with azi- thromycin in treatment of COVID-19	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	Randomized, Parallel group trial	300	1 year	COVID Ordinal Out- comes Scale is defined as: 1. Death 2. Hospitalized on invasive mechanical	6 sites Air Force Hospital Gorakhpur, Uttar Pradesh Air Force Hospital Kanpur, Uttar Pradesh	Government	T

Table 2: (continued)

S. No:	Trial name (scientific name)	Intervention	Study design	No of participants	Duration	Primary endpoint	Site	Sponsor	Preventive (P)/Therapeutic (T)
		HCQ 400 mg BD on D1 and 400 mg OD on D2 – 5				ventilation or extra-corporeal 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)	Base Hospital Delhi Cantt., Delhi Base Hospital Lucknow, Uttar Pradesh Command hospital Lucknow, Uttar Pradesh Military Hospital Ahmedabad, Gujarat		
8	A multi-centre, open label, two arm randomized, pivotal phase 2 trial to study the efficacy and safety of Itolizumab in COVID-19 Complications	Itolizumab 1.6 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	Randomized, Parallel group, active controlled trial	30	3 months	One-month mortality rate between the two arms 1-month mortality is defined as the ratio of patients who will live after 1 month from study start out of those registered at baseline	MAMC medical college and Lok Nayak Jai Prakash Narayan Hospital, Delhi Narayana Health, Karnataka Seth GS medical college and KEM Hospital, Maharashtra	Private	T

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 CTIR 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 (*Mulati*) 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 been 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 of 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 combating 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 CTIR 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

- Lumbreras-Marquez MI, Campos-Zamora M, Lizaola-Diaz de Leon H, Farber MK. Maternal mortality from COVID-19 in Mexico [published online ahead of print, 2020 May 30]. *Int J Gynaecol Obstet* 2020. <https://doi.org/10.1002/ijgo.13250>.
- Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 2020.
- WHO coronavirus disease (COVID-19) dashboard. Available from: <https://covid19.who.int/> [Accessed 2 Jul 2020].
- Iyer M, Jayaramayya K, Subramaniam MD, Lee SB, Dayem AA, Cho SG, et al. COVID-19: an update on diagnostic and therapeutic approaches. *BMB Rep* 2020;53:191–205.
- COVID-19 INDIA. Available from: <https://www.mohfw.gov.in/> [Accessed 2 Jul 2020].
- Gowri S, Kannan S. Clinical trials in dentistry in India: analysis from trial registry. *Perspect Clin Res* 2017;8:95.
- Clinical Management Protocol. COVID-19. Available from: <https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf> [Accessed 2 Jul 2020].
- Karekar SR, Pooja SG, Marathe PA. A review of clinical studies involving pregnant women registered in the Clinical Trials Registry of India. *Perspect Clin Res* 2020;11:8.
- COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. Available from: <https://www.fda.gov/media/137926/download> [Accessed 2 Jul 2020].
- A pilot study to assess the efficacy of ayush-64 in covid-19 cases. Available from: https://mahayush.gov.in/DOA/COVID19_Research/Protocols%20for%20Clinical%20Studies%20and%20Survey%20Studies/Clinical%20protocols/PILOT%20STUDY.pdf [Accessed 2 Jul 2020].
- Chaturvedi S, Kumar N, Tillu G, Deshpande S, Patwardhan B. Ayush, modern medicine and the covid-19 pandemic. *Indian J Med Ethics* 2020.
- Maurya DK. Evaluation of yashtimadhu (*Glycyrrhiza glabra*) active phytochemicals against novel coronavirus. SARS-CoV-2.
- Kaur R, Kaur H, Dhindsa AS. *Glycyrrhiza glabra*: a phytopharmacological review. *Int J Pharma Sci Res* 2013;4:2470–7.
- Sharma R, Martins N, Kuca K, Chaudhary A, Kabra A, Rao MM, et al. Chyawanprash: a traditional Indian bioactive health supplement. Published. *Biomolecules* 2019;9:161.
- Gupta A, Kumar S, Dole S, Deshpande S, Deshpande V, Singh S, et al. Evaluation of cyavanaprāśa on health and immunity related parameters in healthy children: a two arm, randomized, open labeled, prospective, multicenter, clinical study. *Ancient Sci Life* 2017;36:141–50.
- Guidelines for Ayurveda Practitioners for COVID 19. Available from: <https://www.ayush.gov.in/docs/125.pdf> [Accessed on 2 July 2020].
- Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun* 2004;323:264–8.
- Keyaerts E, Li S, Vijgen L, Rysman E, Verbeeck J, Van Ranst M, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. *Antimicrob Agents Chemother* 2009;58:3416–21.
- Gautret P, Lagier JC, Parola P, Meddeb L, Mailhe M, Doudier B, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949.
- Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* [Internet]; 2020, 6:16 p. Available from: <https://doi.org/10.1038/s41421-020-0156-0>.
- Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020:10–0282.
- Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial medRxiv;2020, 03:20040758 p. Preprint. Version 2.
- Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020. pii: ciaa237. <https://doi.org/10.1093/cid/ciaa237>.
- Lenzer J. Covid-19: US gives emergency approval to hydroxychloroquine despite lack of evidence. *BMJ* 2020;369.m1335. <https://doi.org/10.1136/bmj.m1335.32238355>.

25. Indian Council for Medical Research. Recommendation for empiric use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection. Available from: https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf [Accessed 3 Apr 2020].
26. Gautret P, Lagier JC, Parola P, Meddeb L, Sevestre J, Mailhe M, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Trav Med Infect Dis* 2020;34:101663.
27. International clinical trial registry platform. Available from: <https://apps.who.int/trialsearch/Trial2.aspx?TrialID=PER-010-20> [Accessed 2 Jul 2020].
28. Recommendations for investigational COVID-19 convalescent plasma. Available from: <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma> [Accessed 2 Jul 2020].
29. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *J Am Med Assoc* 2020;323:1582–9.
30. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *J Am Med Assoc* 2020: e2010044. <https://doi.org/10.1001/jama.2020.10044>.
31. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res* 2020;178:104787.
32. Miyasaka M. Is BCG vaccination causally related to reduced COVID-19 mortality? *EMBO Mol Med* 2020;12:e12661.
33. Sehgal IS, Bhalla A, Puri GD, Yaddanapudi LN, Singh M, Malhotra P, et al. Safety of an immunomodulator *Mycobacterium w* in COVID-19. *Lung India* 2020;37:279–81.
34. Zhang B, Swamy S, Balijepalli S, Panicker S, Mooliyil J, Sherman MA, et al. Direct pulmonary delivery of solubilized curcumin reduces severity of lethal pneumonia. *Faseb J* 2019;33: 13294–309.
35. Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY, Liu HG, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J Med Chem* 2007;50:4087–95.