An Academic Multicentre Open Label Single Arm Study to Record the Efficacy of Indomethacin among Confirmed COVID-19 patients with Mild and Moderate Symptoms

Brief Summary

This study an open label single arm study to record the efficacy and safety of Indomethacin among hospitalized patients with mild and moderate symptoms confirmed COVID – 19.

At present there is no clear cut guidelines for symptomatic treatment of Covid-19 patients. Paracetamol and cough syrups are widely used. Paracetamol is a weak anti-inflammatory drug and many patients with mild COVID get hospitalised due to symptoms. High risk patients are also hospitalised with mild COVID. This aim of the study is to determine whether Indomethacin a powerful anti-inflammatory drug would rapidly relieve symptoms and reduce hospital stay in such patients.

The present Study is mainly to demonstrate the anti-inflammatory effect and the benefit in mild and moderate COVID 19 patients. So the lowest dose would be tried for the shortest period including high risk patients also.

The postulation is that indomethacin would give rapid relief of symptoms thereby reduce or prevent hospitalisation in mild COVID. If the drug is effective against cough it would also reduce the spread of the disease

Study Procedure

After the consent of the patient, Indomethacin will be administered as per the dosage given below. The enrolled patients are with positive SARS – CoV -2 RT-PCR test results.

Inclusion and Exclusion Criteria of Patients

Inclusion

- Age between 20 and 90 years

- RT – PCR Positive
- Hospitalised patients
- The case criteria for the study:
    - KFT Normal
    - LFT Normal
    - Upto 5 in WHO ordinal scale

Exclusion

- Hypersensitivity / Allergy to Drug
- Gastritis
- Recent Heart attack
- Severe Asthma
- Acute Kidney Injury.
- Patients on immunosuppressants

Study Drug

The recruited patients will be clinically examined and tested and the relevant data entered as given in Table 1. Patients will receive Indomethacin (IR – Immediate Release) 25mg x 2 for five days. The drug dose is less than that recommended in the pharmacokinetic study[1] based on experience and for pragmatic reason. However, if the symptoms persist, the dosage can be changed at the discretion of the treating physician. A pharmacokinetic study recommended 50 mg three-times-a-day for the IR formulation, and 75 mg twice-a-day for the SR (sustained release) formulation for three days. Patients will also receive proton pump inhibitor, omeprazole 20mg one per day. Can be continued for 10 days if symptoms recur after stopping the drug. Paracetamol will be stopped (if given earlier) after the start of Indomethacin.

Table 1. Demographics of COVID -19 patients recruited for trial

Variable	Categories	Number, n	Percentage, %
Age group	18 – 30		
	30 – 40		
	40 – 60		
	60 – 70		
Sex	Male / Female		
Diabetes	Present / Absent		
Hypertension	Present / Absent		
Cardiovascular disease	Present / Absent		
Chronic lung disease	Present / Absent		
Any other Comorb idity	Type		

Study Medication Monitoring and Adverse Event Monitoring

Table 2 describes all the parameters to be recorded during the study. The patients will be monitored on a daily basis for (a) the development of adverse events and (b) for any other side effects and complications that may arise due to the medication

Table 2. Study Monitoring

- Registration no
- Age
- Sex
- Medication already on
- Duration of disease (onset of symptoms)
- Days after the symptom from which the medication was started
- Symptoms
- Cough
- Fever (Temperature)
- Body Ache
- Fatigue
- Oxygen Saturation
- Appetite
- Taste
- Smell
- Gastrointestinal

Lab tests At Admission and Discharge

- C- Reactive Protein (mandatory)
- NLR (optional)
- ESR (mandatory)
- S.FERRITIN (optional)
- LDH (optional)
- Liver Function Test (mandatory)
- Kidney Function (mandatory)

X - ray Chest or CT

- Initial
- At the end of two weeks

Study Endpoints

The primary endpoint is the WHO COVID Ordinal Outcomes Scale at day 14. The details of the endpoint are displayed in Table 3. Secondary endpoints include hospital-free, ventilator-free, and ICU-free days all at 14 days and all calculated as a worst-rank ordinal, in which death is scored as -1, while the lowest score possible for survivors is 0. Time to a 1-point decrease in the WHO COVID Ordinal Outcomes scale and the shape of the WHO COVID Ordinal Outcomes scale over time will also be evaluated.

Ethical Considerations

All ethical considerations, including the protocol and means of collecting data will be reviewed by the ethics committee of the hospital before the recruitment of the first patient.

Table 3. WHO Ordinal Outcome Score*

Patient State	Descriptor	Score
Ambulatory	No limitations of activities	1
	Limitation of activities	2
Hospitalized, Mild Disease	No Oxygen therapy	3
	Oxygen by mask or nasal cannulae	4
Hospitalized, Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Invasive mechanical ventilation without other organ support	6
	Invasive mechanical ventilation with other organ support (e.g., ECLS, CRRT, vasopressors)	7
Death	Dead	8

ECLS: extracorporeal life support;

CRRT: continuous renal replacement therapy

*The score for the day reflects the worst status for the given calendar day

Rationale for open label single arm study of Indomethacin

Paracetamol and cough syrups are widely used to treat COVID – 19 patients. Paracetamol is a weak anti-inflammatory drug and alternative treatment is warranted. Indomethacin is a time honoured anti-inflammatory drug used in rheumatoid arthritis. It has also been used in other inflammatory conditions like pericarditis. Given the pandemic situation and the fact that there are very few trials involving Indomethacin, and answers are sought for alternative treatment, we felt an open label single arm study is urgently required.

Indomethacin acts by reducing prostaglandin synthesis by inhibiting COX1 and COX2 enzymes. COX2 is concerned with the cytokine storm produced by sepsis. Indomethacin was used successfully to prevent cytokine reaction in kidney transplant patients receiving OKT3[1,2]. Its in-vitro antiviral properties for Covid19 has been documented[3]. Its anti - viral activity against SARS has been brought out by Amici et. al[4] . It has no adverse effect on the clotting system[5]. On the contrary it prevents thrombosis in lungs in experiments with septicaemia[6]. The medicine has low side effect profile when used for short periods. It can reduce hospitalisation and spread of the virus by hastening recovery.

Considering the scientific evidence and the low side effect profile a trial with Indomethacin is warranted. A trial in the United States has started a combination trial of indomethacin, HCQS and Azithromycin[7]. 60 patients have been started on indomethacin in New York with promising results[8]. The drug was patented for broad spectrum antiviral properties in 2007[9]. The anti-viral dosing has also been worked out using computational techniques for COVID -19[10].

A recent paper by Marinella has brought out the rational for the use Indomethacin[11]. which Anecdotal evidence has been provided by Dr. Jonathan Leibowitz[12]. A trial in Iran is underway for efficacy and

safety of Indomethacin for treatment for Covid-19 induced pneumonia[13] . A retrospective study with paracetamol instead of indomethacin will serve as the control group. In both cases the standard care as governed by the ICMR protocol will be followed.

Statistical Analysis

A total of 150 patients will be recruited for the study. A broad statistical analysis to be performed are outlined here. This may be subject to changes depending on the nature of outcome and data.

The statistical analysis to be performed can be classified into four parts, namely General, Safety, primary analysis and interim monitoring. This broadly follows the method outlined by Brown et.al[14].

General :

The following summarises the key data from the trial

- Descriptive summaries for relevant variables.
- Primary analysis and analyses of secondary efficacy outcomes to be performed.
- Summaries of safety outcomes will be performed in the safety population consisting of all patients who receive at least one dose of study medication.

Primary Analysis

- Day-10 assessment of the 8-level COVID Ordinal Outcomes
- This analysis will be performed using a proportional odds logistic regression model, taking into account patient age, comorbidities, and the baseline level of the COVID Ordinal Outcomes Scale as covariates.

Safety

Safety features Indomethacin is well understood. Nevertheless, any adverse events in the study will be reported and analysed.

Interim Monitoring

The accumulating evidence provided by the data for treatment benefit or harm will be updated at successive interim analyses as the trial proceeds.

Conclusions

This trial has been envisaged to bring out a cheap and effective treatment for the COVID – 19 pandemic. Indomethacin seems to satisfy scientifically all the requirements to fight the coronavirus and this trial aims to convert the science into a tangible treatment protocol

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