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The Greek study in the effects of colchicine in COVID-19 complications prevention (GRECCO-19 study): Rationale and study design

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A B S T R A C T

Objective: Colchicine has been utilized safely in a variety of cardiovascular clinical conditions. Among its potential mechanisms of action is the non-selective inhibition of NLRP3 inflammasome which is thought to be a major pathophysiologic component in the clinical course of patients with COVID-19. GRECCO-19 will be a prospective, randomized, open-labeled, controlled study to assess the effects of colchicine in COVID-19 complications prevention.

Methods: Patients with laboratory confirmed SARS-CoV-2 infection (under RT PCR) and clinical picture that involves temperature >37.5°C and at least two out of the: i. sustained coughing, ii. sustained throat pain, iii. Anosmia and/or ageusia, iv. fatigue/tiredness, v. PaO2<95 mmHg will be included. Patients will be randomised (1:1) in colchicine or control group.

Results: Trial results will be disseminated through peer-reviewed publications and conference presentations.

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1. Introduction

The COVID-19 pandemic crisis has literally altered the way scientific knowledge is to be discovered and diffused. It is our strong belief that moving into this new era, we should also implement a paradigm shift in research: we should move from open-data to open-research-ideas. In fact, in a time when reliable “cross-checked” results are needed in a time-efficient manner, multiple-input multimodal collaborative projects (a medical research GitHub, if one dares the simile) may be the answer. Therefore, we opted to publish the rationale and design of the present study prior to obtaining its first results.

2. Background

Colchicine is a drug administered for years in various patient settings. It is a classic treatment for acute pericarditis1. Moreover, in the recent ESC guidelines it is suggested that it may be administered for the prevention of post-pericardiectomy syndrome1 and in a consensus document it is suggested that it may be used for prevention of atrial fibrillation recurrence after cardiac surgery or ablation procedures2. Beyond these, colchicine has been administered in numerous research protocols with various clinical settings (including acute myocardial infarction) showing a favorable safety profile and promising results1,4.

As far as patients with COVID-19 are concerned, first reports indicate that myocardial injury is frequently present. In a study from Wuhan, China, in 191 patients, cardiac necrosis biomarkers' elevation was found to be an independent predictor of need for mechanical respiratory support5. In another study from Wuhan, which included 150 patients with COVID-19, 7% of deaths was attributed in myocarditis with circulatory collapse, while in 33% myocarditis had played a crucial role in the final adverse outcome6.

Patients with COVID-19 often develop acute respiratory distress syndrome and/or acute lung injury (ARDS/ALI). Fulminant pulmonary inflammation provokes diffuse alveolar injury resulting in pulmonary infiltrations and, clinically, in acute respiratory failure and it has been reported that myopericarditis is observed in a substantial proportion of hospitalized patients3.

In experimental models it has been shown that inflammasome NLRP3 is a major pathophysiological component in the development of ARDS/ALI3–10, while structural dry-lab models have shown that in the new SARS-CoV-2 proteins such as viroporins E, 3a and 8A play a substantial role in viral replication and pathogenic sequelae11. Additionally, there are data supporting that these three proteins provoke the activation of inflammasome NLRP312–15.

Furthermore, SARS-CoV-2 entry in cells is dependent on the connection of viral proteins S with cellular receptors and activation of viral proteins by proteases of host-cells16,17. Therefore, factors that may have an effect on clathrin-mediated endocytosis (a procedure that is – in part – regulated by microtubules remodeling18) would potentially decelerate viral infection of cells19.

Colchicine is a lipid-soluble alkaloid20, which after oral administration is absorbed in the jejunum and ileum with maximum plasma concentrations achieved after 1–2 hours (after a single p.o. dose). Maximum anti-inflammatory effect develops within a time frame of 24–48h. This time period is required for drug accumulation in granulocytes and monocytes, in which concentrations are several times higher than plasma concentrations21. Indeed, it remains there for several days after last administration22.

Colchicine binds to unpolymerized tubulin heterodimers, forming a stable complex that effectively inhibits microtubule dynamics upon binding to microtubule ends23. Moreover, colchicine is a non-selective inhibitor of NLRP3 inflammasome24. While initially it has been thought of merely as an inhibitor of microtubule polymerization and leucocyte infiltration, it is now presumed that a significant part of colchicine anti-inflammatory action is attributed to inhibition of the NLRP3 inflammasome25. Colchicine inhibits inflammasome on two levels: it inhibits P2X7 receptor activation and ASC polymerization, thereby inhibiting interaction between pyrin-like domains26. Additionally, colchicine suppresses the transport of mitochondria and subsequent approximation of ASC to NLRP3, indicating that microtubules mediated the transport of mitochondria to create optimal sites for activation of the NLRP3 inflammasome27. Colchicine has been shown to limit IL-1β production as a response to various NLRP3 inflammasome inducers in a dose-dependent fashion. For example, in the setting of acute coronary syndrome, colchicine was effective in suppressing inter-leukin IL-1β, IL-18 and IL-6, which was attributed to inflammasome inhibition28–30.

In terms of side-effects, colchicine has been safely administered to patients with myocardial infarction both in the acute phase and later on, in the chronic post-myocardial infarction period31,32.

3. Research hypothesis

Based on the aforementioned data, the question which arises is whether colchicine, administered in a relatively low dose, could potentially have an effect the patients’ clinical course by limiting the myocardial necrosis and pneumonia development in the context of COVID-19. If present, this effect would be attributed to its potential to inhibit inflammasome and (less probably) to the process of SARS-CoV-2 endocytosis in myocardial and endothelial respiratory cells.

4. Patient population

Patients with laboratory confirmed SARS-CoV-2 infection (under RT PCR) and clinical picture that involves body temperature >37.5°C and at least two out of the: i. sustained coughing, ii. sustained throat pain, iii. anosmia and/or ageusia, iv. fatigue/tiredness, v. PaO2<95 mmHg.

5. Exclusion criteria

Pregnancy; known hypersensitivity to colchicine; known hepatic failure; eGFR<20 ml/min; clinical estimation that the patient will require mechanical respiratory support in less than 24 hours; any clinical estimation of the attending physician under which the patient shall be excluded; QTc >450 msec.
6. Study design

Prospective, randomized, open labeled, controlled study. Patients will be randomized in two groups (A and B). Patients of group-A will be treated under optimal treatment based on the algorithm proposed in Greece (as per Ministerial Committee decisions) while in group-B patients on top of this colchicine will be also administered.

6.1. Treatment Arm

On top of usual medical treatment, a loading dose (p.o) of colchicine 1.5 mg (followed 60 min later by 0.5 mg if no adverse gastrointestinal effects are observed) will be administered followed by 0.5 mg colchicine twice a day (except for patients weighing <60 kg in whom 0.5 mg colchicine will be administered once daily). In the case of concurrent treatment with azithromycin as per local protocol then the loading dose of colchicine will be reduced to 1 mg and the maintenance dose will remain unchanged.

6.2. Control Arm

Usual medical treatment only.

7. Endpoints

BIOCHEMICAL “PHASE”
- Time for CRP levels that exceeds > 3xU.N.L.
- Difference in maximum high-sensitivity troponin within 10 days from treatment

8. Clinical “PHASE”

8.1. Primary

Time to clinical deterioration (criterion: 2 levels in WHO R&D Blueprint scale32–34).

8.2. Secondary

- Percentage of patients who will require mechanical ventilation
- Mortality
- Function Lung Tests in healed patients

9. Sample size

For the clinical phase time-dependent univariate COX regression analysis (power 0.8, alpha 0.05) a total of 180 patients was found to be required to detect a hazard reduction of 50% (i.e. hazard ratio = 2 for the group A)35. Due to the pandemic crisis, data will be analyzed every 20 patients who complete the study.

10. Ethics and dissemination

Local Ethics approval has already been obtained in Greece and submission is in process in other participating countries. Trial results will be disseminated through peer-reviewed publications and conference presentations.

11. Trial registration number

ClinicalTrials.gov Identifier: NCT04326790

12. Conclusion

GRECCO-19 trial aims to identify whether colchicine may positively intervene in the clinical course of COVID-19.

Conflict of interest

No conflict of interest exists.

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