CHROLOQUINE PHOSPHATE AGAINST INFECTION BY THE NOVEL CORONAVIRUS SARS-CoV-2 (COVID-19): THE HOPE OPEN-LABEL, NON-RANDOMIZED CLINICAL TRIAL

FINAL CLINICAL STUDY REPORT

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ABBREVIATIONS

FiO_2: oxygen content of the inhaled mixture

pO_2: partial oxygen pressure

AE: adverse event

SAE: serious adverse event

SYNOPSIS

Scope	Humanity has been experiencing a new pandemic of the SARS Coronavirus-19 virus (SARS-CoV-2) since November 2019, which often causes pneumonia and significant respiratory distress. Recent data indicate significant in vitro activity of chloroquine against this new virus. The study aimed to document possible prevention of the development of pneumonia in patients staying at home and in improving the symptoms of SARS-CoV-2 pneumonia in patients who will be hospitalized.
Study design	Perspective, multicenter, open label, phase 2 study
Inclusion criteria	• Age older than or equal to 18 years • Both genders • For women of childbearing potential, they must use or be willing to use a dual contraceptive method during the study. Prior to admission to the study, a pregnancy test will be performed to rule out pregnancy. • Written informed consent provided by the patient or legal representative in case the patient is unable to consent. • Manifestation of upper respiratory tract or lower respiratory tract infection. • Positive test for respiratory secretions for SARS-CoV-2 virus by molecular techniques or positive IgM blood antibody titer.
Treatment	Chloroquine phosphate: The total duration of treatment was 7 days. The dosage was 500mg every 12 hours. It is clarified that any other treatment at the discretion of the therapist is permitted.
Primary endpoint	The achievement of one of the two objectives on day 8 visit after admission to the study: • 50% reduction in symptom score for patients with lower respiratory tract infection • Lack of progression to lower respiratory tract infection in patients enrolled in the study due to upper respiratory tract infection.

Secondary endpoints	• Comparison of the primary endpoint with a group of historical comparators (respective patients not receiving the treatment) • Progression into severe respiratory failure by day 14. For this endpoint a comparison will be made with a group of historical comparators • Frequency of AEs and SAEs
Initial sample size calculation	The power of the study is calculated on the assumption that according to international data, the primary endpoint defined above is achieved in 45% of patients with the natural progression of the disease. In order to achieve this in 70% of patients with chloroquine, 60 patients must be enrolled in the study in order to have an 80% power at a significance level of 10%. It is clarified that if the analysis that will be done after the completion of the integration of 60 patients is positive, with achievement of the primary endpoint, the study will continue with the inclusion of additional patients up to 1000 patients as "compassionate" drug administration.
Final sample size	The study was prematurely terminated with the inclusion of 27 eligible patients
Study duration	1 year

STUDY POPULATION

The study took place during the period May-November 2020 with the inclusion of 29 patients. After November 2020, the investigators did not favor the inclusion of more patients due to the announcement against the administration of hydroxychloroquine by the World Health Organization. Two patients withdrew consent and requested removal of their data. 24 patients completed the 7-day treatment with oral chloroquine phosphate at a dose of 500 mg twice daily orally. Treatment was discontinued prematurely in three patients: in one patient due to development of respiratory failure and the need for mechanical ventilation, and in two patients due to a non-serious adverse event. The total number of patients to be analyzed was 27.

Patient characteristics were as in Table 1 below:

Table 1 Characteristics of the 27 patients during study enrolment

Age, mean ± SD (year)	56.7 ± 14.7
Male, n (%)	19 (70.4)
Inclusion due to upper respiratory tract infection, n (%)	4 (14.8)
Inclusion due to lower respiratory tract infection, n (%)	23 (85.2)
History of comorbidities, n (%)	
Type 2 diabetes	8 (29.6)
Administration of corticosteroids	3 (11.1)
Chronic heart failure	1 (3.7)
Coronary heart disease	1 (3.7)
Chronic obstructive pulmonary disease	2 (7.4)
Solid non-metastatic tumor	1 (3.7)
Obesity	3 (11.1)
Respiratory symptom score, median (minimum-maximum)	2 (0-9)
Respiratory ratio (ratio of partial oxygen pressure / fraction of inspired oxygen), median (minimum-maximum)	326 (261-384)

STUDY ENDPOINTS

Primary endpoint

The primary endpoint of the study is composite and includes the achievement of one of the two objectives on day 8 visit from the inclusion in the study:

- 50% reduction in respiratory symptom score for patients with lower respiratory tract infection
- Lack of progression to lower respiratory tract infection in patients admitted to the study due to upper respiratory tract infection

This was achieved in 23 patients (85.2%) and more specifically in 3 out of 4 patients (75%) who were enrolled in the study due to upper respiratory tract infection and in 20 (87.0%) who were enrolled in the study due to infection of the lower respiratory tract (p = 0.495).

Secondary endpoints

- *Comparison of the primary endpoint with a group of historical comparators*

A group of 90 patients with similar severity characteristics to those of the HOPE study described in a recent publication was selected as a historical comparator group (1). AMong those comparators the primary endpoint was reached at 73.3% (p: 0.304). Comparators were treated with hydroxychloroquine and azithromycin so the result of the absence of a statistically significant difference can be interpreted as non-inferiority.

- *Manifestation of severe respiratory failure by day 14. For this point a comparison was made with a group of historical comparators*

Severe respiratory failure by day 14 was manifested in 3 patients (11.1%). A group of 90 patients with similar severity characteristics to those of the HOPE study described in a recent publication was selected as a historical comparator group (1). Among those comparators, 24 patients developed severe respiratory failure by day 14 (26.7%, p: 0.120). Comparators were treated with hydroxychloroquine and azithromycin so the result of the absence of a statistically significant difference can be interpreted as non-inferiority.

- *Frequency of adverse events (AE) and serious adverse events (SAE)*

Five adverse events were reported; two non-serious events and three serious events.

Three SAEs unrelated to the study drug were identified. All three involved progression into severe respiratory failure with mechanical ventilation. Discontinuation of the study drug was required for one of the patients.

Two non-serious AEs were identified that were possibly related to the study drug. One was an episode of bradycardia and the other was prolongation of the QTc interval on the electrocardiogram. For both patients, it was decided to discontinue the study drug. Both were fully resolved.

CONCLUSIONS

In the open-label, non-randomized HOPE study, the oral administration of chloroquine phosphate to patients with acute COVID-19 infection without respiratory failure:

- Resulted in success of the composite primary endpoint in 82.5% of patients. This corresponds to (a) the absence of progression to lower respiratory tract infection in the case of patients enrolled in the study due to upper respiratory tract infection; or (b) the absence of progression to respiratory failure in the case of patients enrolled in the study due to lower respiratory tract infection. The composite primary endpoint was assessed on day 8 i.e. immediately after completion of treatment with the study drug. The percentage of achievement of the primary endpoint does not differ statistically significantly from that of the historical comparators. Since comparators were treated with hydroxychloroquine and azithromycin, the absence of a difference corresponds to non-inferiority.
- Resulted in progression to severe respiratory failure by day 14, i.e. up to seven days after completion of treatment with the study drug, in 11.1% of patients. This percentage does not differ statistically significantly from that of historical

comparators. Since comparators were treated with hydroxychloroquine and azithromycin, the absence of a difference corresponds to non-inferiority.

- Non-serious AEs possibly related to the study drug were identified in two patients (7.4%), which led to premature discontinuation of treatment.

REFERENCES

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