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A protocol for a multi-centre, double-blinded, randomised, placebo-controlled trial on the efficacy and safety of lopinavir/ritonavir plus ribavirin in the treatment of severe acute respiratory syndrome

Key Message

A protocol for a multi-centre, double-blinded, randomised, placebo-controlled trial on the efficacy and safety of lopinavir/ritonavir plus ribavirin in the treatment of severe acute respiratory syndrome (SARS) was produced. It can be referred to or modified should a future outbreak of SARS occur in Hong Kong.

Introduction

Severe acute respiratory syndrome (SARS) is caused by a novel SARS-coronavirus (SARS-CoV). The clinical and epidemiological diagnostic criteria have been defined by the World Health Organization and laboratory tests including reverse transcription–polymerase chain reaction (RT-PCR), viral isolation, and serology have been developed to confirm the diagnosis.

During the first phase of the illness, SARS patients usually present with fever, respiratory symptoms, and sometimes diarrhoea. Chest radiographs and/or computed tomographic (CT) scans of the thorax show mostly focal and slowly progressive pneumonic and/or ground glass changes. This phase is characterised by viral replication as shown by quantitative PCR tests. Prospective viral load studies in nasopharyngeal secretions from SARS patients revealed that viral replication peaked on the 10th day after the onset of symptoms. When the symptoms of viraemia subsided, there may be a transient period of clinical improvement. During the next phase, a significant proportion of patients develop progressive pneumonia and respiratory deterioration, for which they often received ventilatory support and were admitted to an intensive care unit. Chest radiographs begin to show more extensive involvement with ground glass appearance and dense consolidation. It is believed that this phase is related to immunological over-reaction to viral stimulation by the host's immune system. The majority of patients respond to supportive treatment and recover. When viral replication subsides and the immune reaction is controlled, pulmonary fibrosis may ensue, which especially affects patients experiencing severe pneumonia during the second and third weeks. Such lung fibrosis may lead to long-term impairment of pulmonary function.

The current strategy for specific treatment of SARS includes suppression of coronavirus replication using antiviral agents and modulation of the immune response with corticosteroids or other agents. General supportive care and prevention of complications are also important, as are oxygen supplementation and assisted ventilation in the event of respiratory failure. Use of broad-spectrum antibiotics has also been advocated.

The purpose of this project was to produce a protocol suitable for a randomised controlled trial to determine the efficacy of proposed treatments for SARS, should a future outbreak occur in Hong Kong.

Hypothesis

The severe respiratory complications associated with SARS-related coronavirus infection can be prevented with lopinavir/ritonavir and ribavirin.

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Aims and objectives

To evaluate if early treatment with lopinavir/ritonavir plus ribavirin reduces the development of 'critical SARS' in patients with SARS. The definition of 'critical SARS' includes (1) PaO_2/FiO_2 ratio of <26.7 kPa (<200 mm Hg), and (2) worsening chest radiography compared to that at the commencement of study treatment.

Methods

This would be a multi-centre, double-blind, randomised, placebo-controlled, parallel group sequential study, with the ratio of patients in the treatment and placebo arms expected to be 1:1. Randomisation would be stratified by study centre and centrally organised. For patients in the treatment arm, medications would include (1) lopinavir 400 mg/ritonavir 100 mg orally twice daily, plus (2) ribavirin 2.4 g orally as a loading dose followed by 1.2 g orally every 12 hours.

The duration of treatment was expected to be up to 10 days. Recruitment would continue as long as subjects were available and the required target number had not been reached. Once a patient developed 'critical SARS', he or she would be given treatment at the discretion of the in-charge clinician. Moreover, the patient could be withdrawn from the study at any stage at the discretion of the in-charge clinician, whatever the reason.

Subjects

The sample size was planned primarily for the analysis of the primary outcome, ie development of critical SARS. Based on data from the outbreak in Hong Kong in 2003, around 7% of patients who received lopinavir/ritonavir plus ribavirin developed critical SARS. A 10% difference in the critical SARS rates between the two treatment arms was considered to be minimally meaningful, and the log-rank test was used to detect such differences at an 80% power and a maximum 5% false-positive error rate.

Three interim analyses would be performed using the spending approach for group sequential trials.[1] The information time would be taken as the proportion of patients followed for 12 days, and the spending function would be taken as the power family of first order. Assuming the interim analyses were conducted at equally spaced information time intervals, the drift parameter of the Brownian motion for the group sequential procedures would be 2.9615 using the normalised log-rank statistics.[2] Therefore, the total number of critical SARS patients required was estimated as 40, which amounted to 170 recruited into each treatment arm. Subjects would include males and females, aged 18 years or older. Written informed consent would be obtained.

The actual times of interim analyses might not necessarily coincide with the planned schedule. However, this did not jeopardise the design in terms of power while still preserving the false-positive error rate.[2]

Efficacy measurements

The primary outcome would be the time taken to develop 'critical SARS', defined as (1) PaO_2/FiO_2 ratio of <26.7 kPa (<200 mm Hg), and (2) a worsening chest radiograph. Rescue from the primary outcome would depend on the PaO_2/FiO_2 ratio.

Secondary outcomes would include serial viral load, resort to non-invasive ventilation, resort to intubation, mortality, duration of hospitalisation, admission to and days in the intensive care unit, time to first desaturation (<95% on room air), days on oxygen, duration of virus detection in various clinical specimens, cytokine profiles and immunological responses. Other adverse outcomes would also be logged, including nosocomial infections, pneumothorax, avascular necrosis of bone, and treatment complication, eg anaemia, renal and liver function impairment, and pancreatitis.

Data analysis

Analysis of the development of critical SARS

The analysis would be performed based on the intention-to-treat principle. The log-rank test would be used to examine differences in the critical SARS development rate between the two treatment arms. Three interim analyses would be performed.

Analysis of the PaO_2/FiO_2 ratio

Resort to analysis of the PaO_2/FiO_2 ratio would be performed as the primary analysis, if the sample size required for the analysis of critical SARS could not be attained. Any decision to switch the primary outcome to the PaO_2/FiO_2 ratio would be made without prior knowledge of these ratios.

Apart from the intention-to-treat analysis, an efficacy analysis of the per-protocol set of patients would also be performed. Results from the two analyses would be compared and conclusions drawn. The reduction of corresponding PaO_2/FiO_2 ratios during the first 10 days of active treatment versus placebo would be assessed by independent sample *t* tests, depending on a normal distribution of results. If the normality assumption failed, logarithmic transformations would be considered, and if the latter were not applicable, the non-parametric Wilcoxon rank sum test would be used.

Safety analysis

The safety analyses would deal with serious as well as less adverse events, laboratory result profiles, and the occurrence of all other complications.

Interim analysis

Two interim analyses would be planned for the primary outcome, ie critical SARS development, only. The overall false-positive error rate would be controlled within 5% by using the α spending function approach for group sequential trials.

Manufacturers of trial drugs and placebo

At present, the manufacturers of Rebetol (ribavirin) and Kaletra (lopinavir/ritonavir) are Schering-Plough Corp (NJ, US) and Abbott Laboratories (IL, US), respectively. Placebo would be manufactured by the Hospital Authority Pharmacy, using the image of the respective drug products.

Results

This study focused on the preparation of a randomised controlled trial protocol. As further outbreaks of SARS had not occurred in Hong Kong, the protocol had not been implemented.

Discussion

The full trial protocol was registered with the Hospital Authority (Protocol number CTC0281), after exhaustive documentation of all aspects of the methodology, including the rationale for such a study, the population selection criteria, the treatment plan, procedures, randomisation, blinding/unblinding, concurrent treatment, withdrawal/discontinuation of patients from therapy and assessment of compliance. Efficacy and safety measurements were also described including the evaluation and documentation of adverse events, with details of follow-up procedures. Data management, especially procedures for clarifying implausible, inconsistent, and illegible entries in the Case Report Forms were to be documented. Statistical analyses to be used were described. Detailed instructions on the administration and regulatory processes were also documented.

Conclusion

A protocol for a multi-centre, double-blinded, randomised, placebo-controlled trial on the efficacy and safety of lopinavir/ritonavir plus ribavirin in the treatment of SARS was produced. It can be referred to and modified, if necessary, should a future outbreak of SARS occur in Hong Kong.

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