World Health Organization

WHO R&D Blueprint

COVID-19

Informal consultation on the potential role of IL-6/IL-1 antagonists in the clinical management of COVID 19 infection

WHO reference number

Geneva, Switzerland, 25 March 2020

R&DBlueprint

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

Some evidence suggests that a subgroup of patients with severe COVID-19 might have a "cytokine storm" syndrome.

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.

Data from China from severe patients show an increase of certain cytokines IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ , tumour necrosis factor-a and IL-6 suggesting that mortality might be due hyper pro-inflammatory immune reaction.

OBJECTIVES OF THE CONSULTATION

Key Questions for Experts

1) What data support the hypothesis that IL6 and IL1 inhibition will be helpful not harmful?
2) What evidence is emerging from the field for clinical benefit of IL6/1 inhibition in the treatment of COVID-19?
3) Is there a specific level of COVID-19 severity where IL6/1 antagonists are more likely to be harmful or helpful? What posology should be tested?
4) How could studies be designed to provide the necessary level of certainty of their efficacy and safety?

This Consultation represents an initial step towards the evaluation of IL-6 /IL-1 inhibitors to improve the severe cases of COVID-19. There are ongoing efforts to identify additional candidate therapeutics and to expand the body of evidence available on each of the candidates.

Agenda items

1) Welcome and Goals of Ad Hoc Consultation
2) Pathophysiologic data from COVID-19 that supports hypothetical use of IL6/1i
3) Existing evidence for clinical benefit from investigations.
    a. Italian investigators
    b. Chinese investigators
4) Potential harms form IL6/1 inhibition
5) Information on any ongoing studies
6) Recommendations:

Working group members

Chair: Marco Cavaleri

Name	Position	Institutional Affiliation
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OVERVIEW OF THE DELIBERATIONS

Overall considerations

Tocilizumab is a monoclonal antibody against the interleukin-6 receptor (IL-6R), therefore an immunosuppressive therapy mainly for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis.

Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis in autoimmune diseases, multiple myeloma and prostate cancer.

Anakinra is IL-1 inhibitors binding to the IL-1 receptor. Rilonacept and Canakinumab bind directly to IL-1. Clinically, the major IL-1 inhibitor is Anakinra. Anakinra is a recombinant modified version of the human interleukin 1 used to treat rheumatoid arthritis.

Discussion on the available evidence (Annex I)

1) One this study has been completed in Anhui Province. Researchers retrospectively observed tocilizumab in treatment of 21 patients with severe and critical COVID-19. Seven of the patients were treated in The First Affiliated Hospital of University of Science and Technology and 14 in Anhui Fuyang Second People's Hospital. Clinical data showed that the symptoms, hypoxygenmia, and CT opacity changes were improved immediately after the treatment with tocilizumab in most of the patients, suggesting that tocilizumab could be an efficient therapeutic for the treatment of COVID-19. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans manifested that the lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean, 15.52 ± 8.89%), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated C-reactive protein decreased significantly in 84.2% patients (16/19). Xiaoling et al, 2020
http://www.chinaxiv.org/abs/202003.00026