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

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R&DBlueprint

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to prevent epidemics

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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
Marco Cavaleri	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Eric Pelfrene	Regulator: Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
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Yaseen Arabi	Chairman, Intensive Care Department	King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

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Ross Upshur	Director, Primary Care Research Unit, Sunnybrook and Women's College Health Sciences Centre, Canada Research Chair in Primary Care Research	University of Toronto, Canada
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John Farley	Director, Office of Infectious Diseases	FDA, USA
Philip Krause	Deputy Director CBER/OVRR	FDA, USA
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Michael Kaufmann	Manager- Advisory	PriceWaterhouse Cooper,USA
David Vaughn	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Ken Duncan	Discovery & Translational Sciences team Lead	Bill & Melinda Gates Foundation, USA

Name	Position	Institutional Affiliation
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand
Robert Walker	Chief Medical Officer and Director, Division of Clinical Development	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Julia Tree	Microbiological Services	Public Health England
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Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia
Jacqueline Kirchner	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Elizabeth Higgs	Global health science advisor for the Division of Clinical Research (DCR)	NIH. USA
Helen Rees	Professor, Wits Reproductive Health and HIV Institute	University of Witwatersrand, South Africa
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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

2) The tocilizumab is being used in Italy, unfortunately in most cases is under compassionate use. There is only one clinical trial registered NCT04315480 and there is no preliminary results available.

3) The FDA has approved the initiation of a double-blind, randomized phase III clinical trial (COVACTA) of tocilizumab (Actemra) for use in combination with standard of care. The trial is about to start.

4) Colleagues from China and Italy were invited, however only Dr. Wei-jie Guan, from Guangzhou, China was present at the teleconference on

behalf of Prof Nan-shan Zhong, he summarized during the call the experience with clinical trial registry No.: ChiCRT2000029765 A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). The study is completed but formal analyses have not been reported because not all of the trial data have been fully entered into the database. A total of 63 patients were recruited. However, no further details are known because of the lack of statistical analyses but it is expected that the results from formal analyses will be disclosed soon. Admittedly, there remain some controversies regarding the indications for the use of tocilizumab in patients with Covid-19. One of the main indications would be the patients who have an inflammatory cytokine storm, particularly those who have an elevated level of serum IL-6 (no extensively accepted cut-off values have been endorsed hitherto). It is hypothesized that patients who have higher levels of IL-6 would benefit more from tocilizumab treatment. According to some previous unblinded uncontrolled pilot study, administration of tocilizumab in a single patient who had significantly elevated level of serum IL-6 did benefit from the therapy.

5) There is no evidence of the use of Tocilizumab during SARS or MERS epidemics. There is one retrospective cohort study for influenza, small number of patients (n = 33). IL-6 inhibition by tocilizumab reduced inflammation associated with infection and resulted in mild symptoms during influenza. Leukopenia might be a useful indicator of viral infection, including influenza, during tocilizumab treatment.

6) During the discussion it was highlighted the controversial information coming from China and Italy regarding the IL-6 and other cytokines concentration in severe hospitalized cases. Levels are highly variable in infection, from 10 pg/ml or less to 1.5 million. John Marshall shared information from clinicians in Italy and France where the cytokines levels are not as high is in sepsis. However, Tocilizumab is in wide use in Italy, and they are impressed anecdotally with its effects. They suggest restricting to patients with high IL-6 levels. It might be possible the cytokines levels change rapidly, and it depends on the time of sampling.

Conclusions:

- Given the very limited evidence of the potential benefits of IL-6 inhibitors the group agreed to make a step back and have a group of experts to work in a background paper to describe the rational and justification for the inclusion of these therapies in a RCT.

- It was also expressed, for the prioritization of therapeutics and vaccines there are a set of criteria to make a risk/benefit analysis, the group should also use the same procedure for these therapies. Therapeutic agents such as IL-6/IL-1 antagonists could have inadvertent adverse effects, and at the same time potential benefits in severe hospitalized patients by reducing the risks/effects of inflammatory reaction and the stay in the ICUs. Therefore, risk/benefits analysis should be based on evidence from earlier clinical trials for prioritization of potential interventions to be included in the Core Protocol

- The Tocilizumab is a very limited supply and very expensive, therefore even it shows same benefit would be available for the treatment of large number of patients

PROPOSED NEXT STEPS

- Libby Higgs (NIH) offered to work in a background paper with a group of experts from the University of California, Washington and Vanderbilt University to complete a background document on rationale, hypothesis, risk benefit.

- WHO secretariat will contact the researches in Italy/China using IL-6-I/L-1 antagonist clinical trials or under compassionate to obtain more information about their reasoning and plans, and sharing with the group the synopses or protocols for these clinical trials.

- Search for information from on clinical studies on therapy targeting consequences on endothelial and epithelial cells – heparin and surfactant.

- Members of the expert panel were invited to share with the WHO R&D Blueprint any additional information on IL-6/IL-1 antagonist that should be considered for the next discussion.

- The panel will be convened again in a week to discuss the background paper and the potential inclusion of these therapeutics in the solidarity efficacy trial

Note that above prioritization decisions are preliminary and may change as further information is provided to WHO.

Annex I

Summary Monoclonal Antibodies against IL-6

General Overview:

IL-6 is a cytokine relevant to many inflammatory diseases, therefore mAB against IL-6 have been used as treatments.

Examples: Tocilizumab (Actemra), Siltuximab (Sylvant), Sarilumab (Kevzara)

Mechanism of Action:

Binds the IL-6 receptor

License Details:

Tocilizumab licensed for use against Large-cell lung carcinoma, cytokine release syndrome

Siltuximab licensed for use against Castlemans disease (lymphproliferative disorders)

Sarilumab licensed for use against Rheumatoid arthritis

Supply:

Supplies are limited

Less relevance to LMICs

Safety:

Some reports of increased risk of infection with use. A recent Cochrane review did not show a significant increase in the risk of serious infections in individuals who were receiving tocilizumab as compared with those who were given placebo

https://www.ncbi.nlm.nih.gov/pubmed/21328309

https://www.ncbi.nlm.nih.gov/pubmed/20614469

Clinical Trials:

Disease	Trial Number	Description	Reference
Covid-19	Unknown	**Phase VI trial – COMPLETED** *Tocilizumab (Actemra)* 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). No obvious adverse reactions were observed.	Xiaoling et al, 2020 http://www.chinaxiv.org/abs/202003.00026
Covid-19		**Phase III trial – ONGOING** *Tocilizumab (Actemra)* randomised, double-blind, placebo-controlled Phase III study (COVACTA) to evaluate the safety and efficacy of intravenous Actemra/RoActemra added to standard of care in adult patients hospitalised with severe COVID-19 pneumonia compared to placebo plus standard of care.	https://www.roche.com/dam/jcr:f26cbbb1-999d-42d8-bbea-34f2cf25f4b9/en/19032020-mr-actemra-covid-19-trial-en.pdf
Covid-19	NCT04315480	**Phase II trial – ONGOING** *Tocilizumab (Actemra)*	https://clinicaltrials.gov/ct2/show/NCT04315480?term=tocilizumab&cond=covid-

		Single group assignment, single blind – target size 30 participants. 8mg/Kg dose in patients affected by severe multifocal interstitial pneumonia correlated to SARS-CoV2 infection. Università Politecnica delle Marche Ancona, Italy	19+OR+coronavirus&draw=2&rank=4
Covid-19	NCT04310228/ ChiCTR2000030894	**Phase ? trial – ONGOING** *Tocilizumab (Actemra)* Randomised open label trial – testing favipiravir + tocilizumab vs favipiravir vs tocilizumab Peking University Hospital, China	https://clinicaltrials.gov/ct2/show/NCT04310228?term=tocilizumab&cond=covid-19+OR+coronavirus&draw=2&rank=2
Covid-19	NCT04315298	**Phase II/III trial – ONGOING** *Sarilumab* Randomized, blinded control trial high and low dose vs placebo to assess clinical efficacy.	https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4
Covid-19	NCT04306705	**Retrospective Cohort – NO RESULTS AVAILABLE** *Tocilizumab (Actemra)* Retrospective cohort 120 participants safety and efficacy Tongji Hospital, China	https://clinicaltrials.gov/ct2/show/NCT04306705?term=tocilizumab&cond=covid-19+OR+coronavirus&draw=2&rank=3
SARS	NA	No evidence of clinical trials using mAB IL-6	NA
MERS	NA	No evidence of clinical trials using mAB IL-6	NA
Influenza	NA	Retrospective cohort - COMPLETED *Tocilizumab (Actemra)* IL-6 inhibition by tocilizumab reduced inflammation associated with infection and resulted in mild symptoms during influenza.	Kawada et al, 2013 https://www.ncbi.nlm.nih.gov/pubmed/23070362

Other: Rheumatoid Arthritis	Multiple Studies	*Tocilizumab (Actemra)* Several Phase III trials completed and shown clinical efficacy and good safety profile.	Rueda et al, 2011 https://www.openaccessjournals.com/articles/tocilizumab-for-rheumatoid-arthritis-results-of-the-phase-iii-clinical-trial-program.pdf
Other: Systemic Sclerosis	NA	No evidence of clinical trials using mAB IL-6	https://ard.bmj.com/content/77/2/212

Anecdotal

Disease	Description	Reference
Covid-19	Tocilizumab is in wide use in Italy, and they are impressed anecdotally with its effects. They suggest restricting to patients with high IL-6 levels. The assay may not be widely available, but an acute phase protein such as CRP may reflect its presence – an important question for study.	Prof. J Marshall University of Toronto

In vivo activity:

Disease	EC50/CC50	Animal and Description	Reference
Systemic lupus erythematosus		In our studies, anti-IL-6 mAb treatment not only significantly inhibited *in vivo* anti-dsDNA autoantibody production in NZB/W F_1 mice, but also significantly inhibited *ex vivo* anti-dsDNA autoantibody production by anti-IgM/anti-CD40-stimulated B cells	Liang et al 2006 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1819578/