WHO R&D Blueprint
COVID-19

**Informal consultation on the potential inclusion of Immunomodulators in a clinical trial**

WHO reference number

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

# INTRODUCTION

There are several ongoing studies in China, Italy and Spain using immunomodulators therapies. The rational to use these therapies is to reduce the proinflammatory immunoresponse as a complement to the antiviral therapy. The evidence suggests that in severe cases of COVID-19 pneumonia the level of cytokines is very high - what is called the “cytokines storm”- in particular proinflammatory tumor necrosis factor alpha (TNF-α), and interleukin-1 (IL-1) , IL-6 and IL-18. On the contrary, patients with severe COVID-19 demonstrate remarkably impaired IFN-I signatures as compared to mild or moderate cases.

Unfortunately most of the evidence that is available today is not from randomized controlled trials (RCT), most evidence is from compassionate use, case reports and observation studies. Therefore there is a need to study the role of immunomodulators in a RCT to generate strong evidence of their efficacy for treatment of COVID-19.

# OBJECTIVES OF THE CONSULTATION

There is a long list of potential immunomodulator candidates to be considered for the solidarity trial. Therefore, to facilitate the discussion, WHO secretariat has prepared a list (table) and summary fact sheets for candidates that are being used in some studies.

This call is not aimed at developing a definitive list or a ranking of which products should be considered for the solidarity trial.

The main objective of the call is to start the discussion: make an overview of a long list of candidates, ensure that the secretariat has not missed anything important and start shortening the list as well as discussing the criteria for the selection.

Given the uncertainties of the risk/benefits of these therapies, some of these products may not be considered directly for a phase III trial because of the absence of data, therefore some should be first evaluated in vitro/in vivo or smaller trials.

# Agenda items

1. Welcome and Goals of the Ad Hoc Consultation
2. Overview of different immunomodulators therapies
3. Share the existing evidence (see annexes)
4. Discussion
5. Recommendations and next steps

# 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 |
| Sina Bavari | Independent Consultant |  |
| Karl Erlandson | Interdisciplinary Scientist | Biomedical Advanced Research and Development Authority, US Department of Health and Human Services |
| John Marshall | Co-Director, Critical Illness and Injury Research Centre, St Michael Hospital, Canada | Co-Director, Critical Illness Research, St Michaels Hospital |
| 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 |
| John Beigel | Associate Director for Clinical Research | NIH, USA |
| Thomas Fleming | Professor of Biostatistics | University of Washington. USA |
| John Farley | Director, Office of Infectious Diseases | FDA, USA |
| Regine Lehnert | Regulator | Federal Institute for Drugs and Medical Devices, Germany |
| Steven Kern | Deputy Director, Quantitative Sciences- Global Health – Integrated Development | Bill & Melinda Gates Foundation, USA |
| Monalisa Chatterji | Senior Program Officer, Discovery & Translational Science | Bill & Melinda Gates Foundation, USA |
| David Vaughn | Senior Program Officer | Bill & Melinda Gates Foundation, USA |
| Michael Kaufmann | Manager- Advisory | Price Waterhouse Cooper, USA |
| Robert Walker | Chief Medical Officer and Director, Division of Clinical Development | Biomedical Advanced Research and Development Authority, US Department of Health and Human Services. USA |
| Julia Tree | Microbiological Services | Public Health England. UK |
| Frederick Hayden | Professor Emeritus, Medicine: Infectious Diseases and International Health | University of Virginia. USA |
| 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 |
| Matthew Frieman | Associate Professor, Microbiology and Immunology | University of Maryland School of Medicine. USA |

# Additional experts:

Michael Jacobs, Andrea Antinori, Vicente Estrada, Richard Peto, Peter Smith, Tom Fleming, Uli Fruth.

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Kolawole Salami, Emer Cooke, Deusdedit Mubangizi, Matthias Mario Stahl, Raymond Corrin, Philip Coyne

# OVERVIEW OF THE DELIBERATIONS

**Overall considerations**

WHO secretariat (Dr Uli Fruth) presented a pre-selection of different immunotherapeutics to facilitate the discussion the list is open and members of the groups may suggest other agents to be added.

Products to consider are:

**1- Biologicals:** anti-cytokine/cytokine receptor mAbs (IL-6); TNFa; IFNϒ; GM-CSF; etc., IL-1 receptor antagonist (Anakinra) anti-complement (C5/C5a) mAbs. There are more than 20 years’ experience using TNFa, mAbs in autoimmune inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, psoriasis or ankylosing spondylitis.

IL-6 inhibitor, it is a mAbs does block the receptor. Tocilizumab (Actrema) produced by Roche is the most used in the studies in China, Italy and France. Sarilumab (Kevzara) produced by Sanofi/Renegeron is a mAbs binding the IL-6 directly.

**2- Chemical drugs:** Inhibitors of protein kinases Janus kinases (JAK), mammalian target of rapamycin (mTOR), Bruton´s tyrosine kinase (BTK). Inhibitors of dihydroxyorotate dehydrogenase (DHODH). Inhibitor of phospholipase A2 (Varespladib). Bioactive peptide (Solnatide).

Several protein kinase inhibitors are licensed or are under development for a broad spectrum of conditions, including inflammatory diseases (RA, Crohn´s), hematologic malignancies, or as immunosuppressants, etc.

There is less experience with kinase inhibitor, but Lilli´s batricinib (Olumiant) has been included as an arm in NIAID’s Phase III Adaptive Covid-19 Treatment Trial

Advantages of chemical drugs over biologicals: they are easier to produce and scale up production, do not require cold chain, lower price, administration is generally oral, characteristics are particularly relevant for LMIC.

On the contrary, mAbs are expensive, not immediately available and normally given by IV route.

Discussion on the available evidence

There are very few studies ongoing with TNFα and ACE-2 receptors antagonist, it is important to consider these type of products, the relevant role in the pathophysiology and the biologic mechanism of harm associated with COVID-19 infection.

Kinasa inhibitors like Batricinib were included in the NIAID trial because it has an antiviral effect (tested in vitro by Emory), is licensed in many countries, widely available, millions of courses are produced in a year and it is relatively cheap. In addition, there were 2 cases treated with rapid improvement. The current trial is with Remdesivir in both arms and Batricinib in one arm. It has a short half-life- in case of sepsis treatment can be stopped and the drug is cleared rapidly. There are some safety concerns with long treatments, the drug has been associated with thrombosis and embolism which is particularly relevant in COVID-19.

There are several ongoing trials with immunomodulators, but looking at clinical improvement end points and progression of the disease in the ordinal scale. Only the solidarity trial has mortality as primary end point, therefore once clinical data from these studies show clinical benefit, these therapies could be included in the solidarity trial. After 20 years of studies immunomodulators therapies have not shown strong benefits and some have shown harm like microangiopathies and in-situ clotting. Autopsies made in NY city showed massive clotting within the organ damaged, consequently clotting and thrombosis should be the clinical priority to treatment.

Since there are no ongoing trials with TNFα, it may be useful to search the registry that the British society of Rheumatology. There may be data that could suggest whether TNFα inhibitors might be worthwhile. So, there might be additional retrospective, coincidental clinical data that would be useful to assess if TNFα inhibitors should be tested in some pilot studies. For instance, there are patients under treatment with TNFα for rheumatoid arthritis, oncology leukemia, therefore it would be interesting to see what would be the outcome of this population regarding COVID-19.

Anti-complement C5 called Zilucoplan (formerly known as RA101495) is not in the table provided by the secretariat, it is an artificial peptide that binds to complement 5 (C5), inhibiting its activity and preventing the overactivation of the complement system — administration is subcutaneous, it is easier administer than mAbs. It is now in phase III for treatment of myasthenia gravis.

We need to have more information about the role of C5 in the pathogenesis of COVID-19 before considering antagonist therapies. It seems that patients in France have high level of Complement, the reports have not been yet published. There are some pre-clinical data in mice (also from MERS) suggesting there may be some benefits of the type of C5 antagonists. There is a small ongoing clinical trial in Europe testing anti-complement therapeutics.

Nafamostat (serine protease inhibitor and anticoagulant), Camostat and anticoagulant (heparin) are not immunomodulator therapies, but members suggested they be considered as well in future discussions. There are several trials in Europe with Camostat/Nafamostast in combination with HCQ/AZM (Denmark, Germany, USA). There are might be some supply/availability issues since it is only approved in Japan and South Korea. Administration could also be problematic given the very short half-life in plasma and to reach an effective concentration.

Colchicine could be also added to the list. It is widely available, easy to produce and not expensive. There are clinical trials in Italy and Canada.

Human recombinant GM-csf should be also added to the list.

Conclusions:

There are many studies ongoing in Europe (Italy and Spain) testing different types of immunomodulators. IL-6 inhibitors (e.g. Tocilizumad) are the most used in trials, preliminary results from a RCT in France shows some effect <https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19>. Though Sarilumab did not show a clear clinical benefit. <https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2020/2020-04-27-12-58-00-2022288-en.pdf>

There are some safety concerns about the use of immunomodulators, these immunotherapies have been approved for other diseases in a different context, and there are some risks in the context of severe pneumonia.

Current clinical trials in Italy and Spain showed an increase of infections, however these data are not being collected systemically since is not the main objective of the study. We also need to consider which population would really benefit for the type of therapies. However, these therapies may have some benefits in specific patients populations treated at the right stage of illness and this emphasizes the importance of having good quality of data from RCTs.

The Clinical Trial design Working Group will have a TC on 7th May to review the Solidarity protocol and discuss whether it needs to be adjusted if a new arm with immunomodulators would added including safety as an outcome.

The secretariat reminds to the members of the WG that the main objective of the call was not to make any choice at this stage, it is a preliminary step to develop a landscape of immunomodulator therapies.

# PROPOSED NEXT STEPS

1. The secretariat will update the list with the therapies suggested during the call. (Famotidine, Leronlimab, Zilucoplan, GM-csf)
2. Members of the group should provide feedback in writing to the secretariat on what products would be the most suitable to further investigate/discuss, what should not be considered and provide the rationale. Members prioritize the list before the next call.
3. In a second round with a shorter list we can create a ranking to select the therapies for clinical trials
4. Next call in a week time.

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

# ANNEX – Criteria for prioritization

Prioritisation Therapeutics

|  |  |  |
| --- | --- | --- |
| **Attribute** |  |  |
| **Basic criteria** | ***[name of drug]*** |
| **Preclinical efficacy data in non-human primates (NHP)**  | Pre-clinical efficacy in NHP under well-controlled and documented conditions* Evidence of efficacy should include improved survival of COVID-19 inoculated rhesus macaques (or other NHPs) following treatment with the drug versus controls.
 |  |
| **Safety profile from non-clinical studies**  | In the absence of human data, safety results from animal studies, as well as relevant in vitro data should be assessed with respect to safety in humans. |  |
| **Quality of manufacturing (cGMP)** | It is expected that the product will be manufactured in compliance with GMP (Good Manufacturing Practice).* Information on the active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) preparation, FPP composition, controls (specifications), known and potential impurities, as well as stability data supporting a reasonable shelf-life should be provided.
* A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the safety/efficacy profile of the product should also be provided.
 |  |
| **Prioritization criteria** |  |
| **Scientific rationale for use in COVID-19 patients** | Brief description of the biological mechanism targeted by the drug. In case of a drug that is approved, or has a large clinical trial experience base, for another indication: explanation of why this is an indicator of success for COVID-19 (e.g. in the case of targeting pulmonary pathologies) |  |
| **Safety in humans single/repeat dose escalation** | Evidence of acceptable risk-benefit profile, i.e. acceptable incidence of SAE, SUSARs or severe AEs with sequelae observed as documented by the DSMB.* Phase 1 clinical data should available for the drug at the exposure level proposed for treatment of COVID-19
* If evidence on dose escalation is available that would be an advantage.
* If human PK trials or studies in other indications at the exposure level proposed for treatment of COVID-19 have been conducted, assessment of safety using standard parameters (adverse events, clinical laboratory monitoring, etc.) will serve as the most meaningful assessment of safety.
* Clinical data supplemented by customary non-clinical at different exposure levels.
 |  |
| **Time-efficacy window after challenge in animal models** | Pre-clinical efficacy in NHP under well-controlled and documented conditions. * Evidence of efficacy should include improved survival of COVID-19 virus inoculated rhesus macaques (or other NHPs) following treatment with the drug versus controls. Surrogate markers, validated or reasonably expected to predict efficacy, e.g. viral load decreases, would be supportive.
 |  |
| **Dosing rationale** | A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be effective in suitable animal models.* Ideally, human pharmacokinetic data would be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels seen in NHPs successfully treated with the drug.
 |  |
| **Route of administration and administration challenges**  | What is the route of administration.* Over how long must the drug be administered, and
* How many administrations are required to complete one treatment course?
 |  |
| **Efficacy data in humans against COVID-19** | Where clinical efficacy data from randomized controlled trials (RCTs) are available, this is clearly preferable to efficacy in animals.* Administration through MEURI does not generate useful information to support clinical efficacy determination due to the very high risk of bias and confounding factors.

Surrogate markers, validated or reasonably expected to predict efficacy, e.g. viral load decreases, would be supportive.Information on combination with other agents, documented or potential drug and/or vaccine interactions would be desirable. |  |
| **Access in event of success****(mandatory)** | Evidence that at least 200 treatment courses compliant with GMP will be available and labeled by the trial initiation date (Evidence that sufficient numbers of GMP treatment courses doses (>200) will be available for early implementation for confirmed cases (by May 2020)Evidence that production plans are in place to meet the treatments supply demand (thousands of doses) in large-scale implementation in at-risk countries in Africa starting in October 2020.Evidence of willingness to ensure that therapeutics will be manufactured and made available to WHO and the public health sector of the COVID-19-affected countries in sufficient amount and at an affordable price. |  |
| **Additional prioritization criteria** |  |
| **Staff training** | Information on the specific training that medical staff would need to have received in order to safely and reproducibly administer the agent. |  |
| **Administration and monitoring equipment** | Is specific equipment that would not normally be present at COVID-19 ICUs needed to administer the agent?Is specific equipment that would not normally be present at ICUs needed to monitor the agent including laboratory equipment for e.g. hematology, biochemistry (e.g. liver, renal function). |  |
| **Storage & shelf-life** | Temperature, stability at given temperature |  |
| **Total** |  |  |

Origin of data: Data and evidence necessary to score the attributes will be collected from published data and information provided by the respective manufacturers.

Weighting/scoring: Scoring: Score 0 to 3 per attribute (0 = no data available; 1= does not meet minimally acceptable profile; 2=meets minimally acceptable profile; 3 likely to exceed minimally acceptable profile). Descriptive attributes are not weighted.

Output: The process based on this framework will result in a report describing the outcome of the assessment of available COVID-19 investigational therapeutics for use by the committee to make the formal decision on recommendations for inclusion in clinical trials at a given point in time. Such decisions are to be revisited upon emergence of significant new information