Position Statement - Specific Treatments for COVID-19

At present, there are no proven pharmacological therapies for prevention or treatment of the COVID-19 respiratory disease that is caused by the novel coronavirus SARS-CoV-2.

ASCIA acknowledges the urgent need for effective therapies for the prevention and treatment of COVID-19.

As the situation regularly changes this document is reviewed and updated as required.

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Pharmacological treatments for COVID-19 can be divided into two classes:

- Antiviral therapies -
  - Pharmacological, e.g. remdesivir, lopinavir/ritonavir, chloroquine/hydroxychloroquine (may also be immunomodulatory)
  - Biological, e.g. convalescent serum (see ASCIA Position Statement on Immunoglobulin Therapies for COVID-19)
- Immunomodulatory therapies -
  - Anti-interleukin-6 (Anti-IL-6), e.g. tocilizumab, siltuximab, sarilumab, JAK inhibitors (see below)
  - Corticosteroids (see below)
  - Anti-interleukin-1 (Anti-IL-1), e.g. anakinra
  - Intravenous Immunoglobulin G (IVIg) - *NOT recommended* (see ASCIA Position Statement on Immunoglobulin Therapies for COVID-19)

ASCIA is aware that many clinical trials are underway in Australia and internationally, and a number of resources are available to access details (e.g. https://clinicaltrials.gov/ct2/results?cond=COVID-19).

The aim of these trials is to provide clinical evidence for safety and efficacy of medications for the prevention and/or treatment of COVID-19.

In the interim ASCIA does not usually recommend the off-label use of medications for the prevention or treatment of COVID-19 outside of these trials, for the following reasons:

- Uncertain benefits.
- Potential risk of harm.
- Impact that inappropriate use of these medications has on continuity of supply for patients with immune diseases for which these medications are established treatments.

Whilst ASCIA recommends that experimental therapies for COVID-19 should be administered in the context of a clinical trial where available, it is recognised that circumstances may arise where this is not possible. ASCIA advises that treatments that lack robust supportive evidence of safety and efficacy in this setting should be considered with appropriate expert consultation.

The role of immunomodulation in COVID-19

Current management of COVID-19 is largely supportive, with respiratory support in cases that develop COVID-19 related acute respiratory distress syndrome (ARDS). However, despite usual ventilation strategies, mortality remains high[1]. There are also reports of the ARDS being unusual and not responding to usual methods of ventilation[2].

Alternative hypotheses have been suggested to explain this phenomenon. Largely this is biologically explained by a cytokine storm syndrome[3].

IL-6 blockade

Based on the understanding of the possible contribution a cytokine storm syndrome to the increased mortality in COVID-19 related ARDS, IL-6 blockade may be beneficial. IL-6 is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine.

Tocilizumab (Actemra) is an inhibitory IL-6 receptor monoclonal antibody that has an established role for the treatment of life-threatening cytokine release syndrome caused by chimeric antigen receptor (CAR) T-cell therapy[4].

ASCIA recommends that IL-6 inhibitors, such as tocilizumab, should be considered as an off-label treatment option for patients with COVID-19-related ARDS, and for use in clinical trials.

This recommendation is based on the confirmed efficacy of tocilizumab in a condition with similar pathogenesis[4,5], and the following clinical reports suggesting benefit in patients with COVID-19:

- The Society for Immunotherapy of Cancer statement on access to IL-6-targeting therapies for COVID-19[6]
- Michot et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report. Annals on Oncology 2020[7]
- Xu et al. Effective Treatment of Severe COVID-19 Patients with tociluzumab[8]

There are also a number of hospital specific and national protocols that include consideration of anti-IL-6 monoclonal antibodies. These data favour the use of IL-6 inhibitors, such as tocilizumab, as an intervention to prevent progression of COVID-19 pneumonia, which may prevent ICU admission and ventilation.

There is no clear evidence for increased risk of infection with short-term use of tocilizumab[9]. The rate of bacterial infection attributable to long-term tocilizumab use in rheumatoid arthritis is approximately one infection per 100 person-years of treatment[10].

Timing for administration of immunomodulatory therapies is likely to be critical to their potential effectiveness. Where tocilizumab is administered for COVID-19 related ARDS, it is recommended that treatment should be considered early in severe disease.

Corticosteroids

During previous coronavirus epidemics, SARS and MERS, corticosteroids were a mainstay of therapy, apparently improving fever and radiographic appearances[11]. However, a systematic review[12] reported no benefit in SARS, and possible harms, including delayed viral clearance associated with corticosteroids administered early in disease course[13]. Data from MERS also suggested no benefit and a possible delayed clearance of virus[14].

On this basis, ASCIA supports the current World Health Organisation (WHO) advice “Do not routinely give systemic corticosteroids for treatment of viral pneumonia outside clinical trials”[15]. However, data from SARS and MERS was generally low quality with small patient numbers. Therefore, ASCIA supports the process of enrolling patients into controlled trials of corticosteroids at different times during the disease course, to determine if these common and inexpensive medications might have a potential role in COVID-19.

Recommendations

1. ASCIA strongly endorses a collaborative, multidisciplinary approach to management of COVID-19.
2. ASCIA recommends that clinicians in all specialties involved in the care of COVID-19 patients consider the use of tocilizumab (an inhibitory IL-6 receptor monoclonal antibody) early in critically ill patients, in consultation with a clinical immunologist or other specialist with experience in use of immunomodulatory therapies for systemic inflammatory diseases. Through its membership of clinical immunology specialists in Australia and New Zealand, ASCIA is available to facilitate consultation and collaboration if needed, regarding the administration of tocilizumab for COVID-19.
3. ASCIA does not currently recommend the use of corticosteroids or anakinra outside of clinical trials. However, there may be exceptional circumstances in which administration of these agents may be considered outside a clinical trial, with appropriate expert consultation.
4. ASCIA actively recommends against the use of IVIg until data emerges of a potential benefit.
5. Consideration of using any treatments for COVID-19 (including tocilizumab) must balance potential clinical benefits with the theoretical risk of harm.

Further information

The situation regarding COVID-19 is rapidly changing, so it important to monitor information from ASCIA other organisations, Australian and New Zealand governments, that are available on the ASCIA COVID-19 webpage www.allergy.org.au/members/covid-19, which is reviewed daily and updated as required.

References

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