TARGETED MONOCLONAL ANTIBODIES

a. ANTI-GM-CSF or GM-CSF INHIBITORS

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Introduction

GM-CSF is a hematopoietic growth factor. Its inflammatory activity is primarily due to its role as a growth and differentiation factor for granulocyte and macrophage populations.[1]

It is one of the key molecules involved in the cytokine storm seen among COVID-19 patients.[2]

Mechanism of Action

GM-CSF is a crucial initiator in the systemic inflammatory pathway driving the chimeric antigen receptor T cell (CAR-T) associated cytokine release syndrome (CRS). [3] It enhances proinflammatory cytokine production, antigen presentation and phagocytosis, and promotes leukocyte chemotaxis and adhesion.[4]

Overexpression of GM-CSF is associated with several human pathologies such as rheumatoid arthritis, multiple sclerosis, juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML). [5]

GM-CSF neutralization prevents CD14+CD16+ inflammatory myeloid cell activation and reduces all downstream monokine production.[6] Blockage of this growth factor may halt the immunopathology caused by the virus.[7]

Lenzilumab is a humanized monoclonal antibody (class IgG1 kappa) designed to target and neutralize GM-CSF. It is currently being evaluated as a potential treatment for JMML & CMML.[8]

Otilimab is a fully human antibody directed against GM-CSF. It is an investigational drug for rheumatoid arthritis and multiple sclerosis.[9]

Mavrilimumab, a human monoclonal antibody, targets GM-CSF receptor α. It is an experimental drug for rheumatoid arthritis.[10]

Clinical Studies

There are no published studies on the efficacy and safety of GM-CSF inhibitors for the management of patients with COVID-19.

Clinical trials on Lenzilumab, Otilimab, Mavrilimumab and another GM-CSF inhibitor, TJ003234, are currently registered for the treatment of COVID-19 infection. [11]

Recommended Dose

No dose provided.

Adverse Effect

Further studies are needed to determine any adverse reactions from GM-CSF inhibitors.

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy and safety of GM-CSF inhibitor to treat COVID-19 infection.

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b. ANTI-INTERLEUKIN-1 (IL–1) or IL–1 INHIBITORS

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Introduction

Interleukin-1 (IL-1) is a pro-inflammatory cytokine released by cells of the innate immune system after exposure to pathogenic organisms whether viral, fungal or bacterial.[1] IL-1β is one of 2 ligands of IL-1 and is one of the most powerful pro-inflammatory cytokines; though it has protective actions against infections, it is also capable of inducing several detrimental biologic processes such as apoptosis, pyroptosis and cell proliferation which can cause tissue damage and organ dysfunction in the host. Its pro-inflammatory activity is regulated by inflammasomes which inhibits IL-1 transcription and processing intracellularly, and, thus, further suppresses hyperinflammatory states.[2,3]

Mechanism of Action

IL-1 antagonists work by capturing IL-1β and hindering it from binding to the IL-1 receptor, hence preventing the pro-inflammatory cascade. Due to their IL-1 antagonistic effects these can interfere with the immune response.

1. Anakinra is the recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1RA) which prevents the binding of IL-1α as well as IL-1β to IL-1R1. It has been approved by the US Food and Drug Administration and the European Commission for the treatment of patients with active rheumatoid arthritis (RA). In RA, studies have indicated that anakinra has a favorable risk–benefit profile. It has a relatively short half-life of 4 to 6 hours; compliance was reported to be high even with daily subcutaneous injection regimen.[4]
2. Rilonacept is a recombinant humanized monoclonal antibody that has a high affinity for IL-1 and potently inhibits its activity. It is administered subcutaneously beginning with a loading dose followed by a weekly injection of half the loading dose. They are indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome in adults and children aged 12 years and older.[5]
3. Canakinumab is a specific human monoclonal IgG1 antibody targeted against IL-1 β. It is also indicated for the treatment of CAPS.[6]

IL-1 And COVID-19

IL-1 has been noted to be over-expressed in SARS-CoV. In COVID-19 disease, the virus binds to toll-like receptors (TLRs) which activate the IL-1 inflammasomes producing more IL-1β in a dysregulated manner. IL-1β facilitates the hyperinflammatory reaction in the lungs, fever and fibrosis causing respiratory complications in the host.[7]

Clinical Studies

Since COVID-19 can present with hyper-inflammation, the use of an interleukin-1 receptor antagonist, anakinra, has been proposed. This is based on a re-analysis of data from a confirmatory Phase III trial, which was a prospective, randomized, double-blind, placebo-controlled, multicenter study. It looked at therapeutic efficacy and safety of an IL-1RA as an adjunctive treatment in patients with severe sepsis. It was given as 100 mg IV bolus and followed by a 72-hr continuous intravenous infusion at 2.0 mg/kg/hr. This study was terminated after the second interim analysis failed to show a statistically significant decrease in mortality.[8] A re-analysis of the study data, done 19 years later, looked at the efficacy of anakinra (recombinant IL-1RA) in improving 28-day survival in sepsis patients with features of macrophage activation syndrome (MAS). Using multiple regression analysis, it was shown that among patients on anakinra the adjusted odds of 28-day mortality is 87% lower than those on placebo [OR for death 0.13 (0.03–0.71), p = 0.018], after controlling for covariates (age, AKI, ARDS).[9]

When the COVID-19 pandemic started, Monteagudo et al. published a retrospective chart review involving five patients diagnosed with MAS (not due to COVID-19) who were given continuous IV infusion because of worsening clinical status. Four of the five patients had rapid serologic then clinical improvement.[10] Another retrospective chart review of all anakinra-treated MAS patients showed that (≤5 days hospitalization) earlier initiation of anakinra was associated with reduced mortality (p=0.046).[11]

Since then, case reports of patients with COVID-19 treated successfully with anakinra have been published. One was on a patient who refused ventilatory support,[12] the next was a patient with hepatic involvement,[13] another with complicated pericarditis,[14] another one with steroid intolerance,[15] and the last one was a patient who was refractory to antivirals and anti-IL-6.[16]

Several case series have also been published. First, a prospective case series of 9 consecutive moderate to severe COVID-19 pneumonia patients at high risk of worsening were given anakinra for 10 days. Results showed good clinical and biologic outcomes for 8 of the 9 patients.[17] Next was a case series of 5 patients who had resolution of systemic inflammation and improvement in respiratory parameters.[18] Anakinra was likewise shown to be safe in 3 patients with acute leukemia and COVID-19.[19] A retrospective case series showed that early initiation of anakinra prevented mechanical ventilation because all 7 of those who were given anakinra less than 36 hours after onset of acute hypoxic respiratory failure did not require mechanical ventilation; 4 patients who were given anakinra after 4 days required mechanical ventilation, 3 were eventually extubated but 1 died. Three patients met their inclusion criteria but were not given anakinra; all 3 also required mechanical ventilation.[20] Another case series of 8 patients with COVID-19 who had secondary hemophagocytic

lymphohistiocytosis reported improvement in respiratory function at the end of treatment (7 days) although 3 later died of refractory shock; the authors reported that the mortality was still lower than historical series of patients with sHLH in sepsis.[21] (Appendix 12-A)

A retrospective cohort of severe COVID-19 patients given anakinra was compared to historical control. Result showed that the need for invasive mechanical ventilation or death occurred in 13 (25%) of 52 patients in the anakinra group compared with 32 (73%) of 44 patients in the historical group (HR 0.22 [95% CI 0.11–0.41; p<0.0001).[22] Another retrospective cohort study included 29 patients in the high dose anakinra group, 7 patients in the low dose anakinra group and 16 patients in the standard treatment group. At 21 days, survival was 90% in the high-dose anakinra group and 56% in the standard treatment group (p=0.009). Treatment with low dose anakinra was stopped after 7 days because of paucity of effects in CRP and clinical status.[23] The most recent study is a small cohort of 12 COVID-19 pneumonia patients who received anakinra early (between the 5th and 13th day of diagnosis); their matched control group were patients who received standard of care. Clinical improvement was observed in the patients who received anakinra.[24] Lastly, there is one retrospective cohort which compared anakinra to tocilizumab. Results showed that the risk of death was lower in the anakinra group (22.0%) than the tocilizumab group (46.2%); the percentage of anakinra treatment responders was correspondingly higher (63.4% vs 43.2%). However, the authors saw that there was a survival advantage with anakinra compared to tocilizumab treated patients. After adjustment for multiple baseline imbalances this difference did not reach statistical significance (PS-adjusted HR=0.46, 95%CI= 0.18-1.20, p=0.11).[25]

Based on these observational and small cohort studies, reliable conclusions cannot yet be drawn with regards anakinra's efficacy and safety; stronger evidence with clinical trials are needed. There are currently 15 clinical trials registered in ClinicalTrials.gov using anakinra, alone or in combination with other immunomodulators, for COVID-19[26] and 4 studies using canakinumab.[27]

Recommended Dose

In various ongoing clinical trials (in ClinicalTrials.gov[26,27]), the following are the dose ranges used:

Anakinra: 100 mg - 400 mg / day IV (with varying duration)
100 mg / day SC (also with varying duration)
2-4 mg/kg/dose (max 100 mg) IV/SQ Q6-24 hours (for HLH/MAS)[28]

Canakinumab: 300 mg - 600 mg / day IV (single dose); one study gave it SC (no dose and duration mentioned)

Adverse Effects

The most frequently reported adverse events were injection-site reactions.[5] An increased frequency of infections has been reported with anakinra use similar to other biologic agents. Opportunistic infections though are rare in anakinra-users. Due to its short half-life and duration of activity, it is considered to be safer than other biologic agents even if given for long term subcutaneous use.[1] In the study by Monteagudo et al., all 5 patients developed cytopenia with IV infusion which could be due to the known clinical course of MAS or due to high dose anakinra since in one patient the cytopenia returned to normal after dose reduction.[10]

Conclusion

Published studies for IL-1 receptor antagonists are limited to anakinra. The use of anakinra to prolong survival in cytokine storm syndrome (CSS) are either observational studies or small cohort studies; hence, its use for COVID-19 CSS should still be in the context of a clinical research, pending results of large clinical trials.

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c. ANTI-INTERLEUKIN 6 (IL–6) or IL–6 INHIBITORS

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Introduction

IL-6 and IL-1 are two of the main pro-inflammatory cytokines released during a viral infection. IL-6 seems to hold a key role in cytokine storm pathophysiology since highly elevated IL-6 levels are seen in patients with cytokine storm.[1] In severe or complicated cases, they were almost three times higher than the non-severe cases.[2,3,4] The use of IL-6 inhibitors in the management of patients with COVID-19 may ameliorate the severe damage to the lung caused by the cytokine release.

Mechanism of Action

The IL-6 inhibitors (tocilizumab, sarilumab and siltuximab) bind to both the membrane-bound and soluble forms of IL-6 receptors thereby blocking the classical and trans signal transduction and its mediated immune response.[5]

Tocilizumab is a recombinant human IL-6 monoclonal antibody that has been approved for rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systematic juvenile idiopathic arthritis. It is already approved by the FDA for the treatment of cytokine release syndrome (CRS) that is severe or life-threatening. The agent is used in adults and children aged 2 years and older who have CRS caused by Chimeric Antigen Receptor (CAR) T-cell therapy.[6]

Siltuximab is a chimeric monoclonal antibody approved for treatment of adults with multicentric Castleman's disease who are human immunodeficiency virus and human herpes virus-8 negative.

Sarilumab is a human IgG1 monoclonal antibody that has been approved by the FDA for rheumatoid arthritis.

Clinical Studies

There are no published clinical trials on the efficacy and safety of IL-6 inhibitors for the management of patients with COVID-19.

There are 14 observational studies , 1 case report and 64 registered clinical trials on the use of tocilizumab for COVID-19 patients. (Appendix 12-B). Two clinical trials were completed and pending publication of results.

A multi-site, randomized, double-blind, placebo-controlled phase III study evaluated the safety and efficacy of intravenous tocilizumab added to standard of care in adult patients hospitalized with severe COVID-19 associated pneumonia compared to placebo plus standard of care (NCT04320615). Initial results of this study showed no improvement in the clinical status of those who received tocilizumab compared to those who received the placebo (OR 1.19; 95% CI 0.81-1.76). Time to hospital discharge was shorter in patients treated with tocilizumab (median 20 days; 95% CI 17-27) than in those treated with placebo (median

28.0; 95% CI 20.0, NE) (p=0.0370). No new safety signals were identified in the study.[7]

In a phase 2, non-randomized, open-label trial, 32 adult patients with COVID-19 were given low-dose tocilizumab (NCT04331795).[8] The patients included in the trial were those with radiographic pulmonary infiltrates, fever, CRP of ≥ 40 mg/L, and did not require mechanical ventilation. Rapid resolution of fever and CRP decline were observed in majority of those who received tocilizumab (40-200 mg) compared to the retrospective controls.

Tocilizumab was given to 21 patients with severe or critical COVID-19 pneumonia. The body temperature of all patients returned to normal after one day of tocilizumab. Majority of the patients had improvements in their peripheral oxygen saturation, CRP levels and chest CT scans.[9]

In a prospective open, single-arm multicenter study of 63 patients with severe COVID-19, the use of tocilizumab within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2; 95%CI 1.3–6.7).[10]

A single-center case-control study on the use of siltuximab in adult COVID-19 patients with ARDS is ongoing (NCT04322188). Interim data showed reduced need for ventilation for most of the included patients.[11]

At present, there are no data from clinical trials on the efficacy of sarilumab for patients with COVID-19. There are 5 registered studies in Clinicaltrials.gov on the efficacy of sarilumab in adult patients hospitalized with severe COVID-19 pneumonia.

The Chinese Clinical Guidance for COVID-19[12]and the Italian Society of Infectious Diseases and Tropical Diseases COVID-19 Guideline[13] have recommended the use of tocilizumab as a treatment option for patients with severe COVID-19.

Recommended Dose

A. Tocilizumab:
   Adult dose:
   - 8 mg/kg (maximum: 800 mg/dose) as a single dose; may repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve[14]
   - 4-8 mg/kg single dose or 400 mg IV diluted in 0.9 NS to 100 ml, given as a 2-hour infusion; a single extra dose may be given after 12 hours at the discretion of the provider[15]

   Pediatric dose:
   - 8 mg/kg/dose IV once; an additional dose may be given 12 hours after the first if clinical symptoms worsen or show no improvement maximum dose: 800 mg/dose[16]

B. Sarilumab: 400 mg single IV dose or 200-400 mg SC dose[17]
C. Siltuximab: 11 mg/kg infused over one hour with a potential second dose at the physician's discretion[11]

Adverse Effects

In the observational study for COVID-19 patients, there have been no reports of subsequent pulmonary infection, deterioration of illness nor death among those given tocilizumab. There were likewise no adverse drug reactions reported.[9]

Tocilizumab was associated with an increased risk of infectious respiratory adverse events in patients with rheumatoid arthritis.[18] Both tocilizumab and sarilumab carry FDA black box warnings of serious infections, such as tuberculosis and invasive fungal infections, leading to hospitalization or death.

Conclusion

Initial results of the completed phase 3 clinical trial on tocilizumab showed no clear clinical benefit for severe COVID-19 pneumonia. There is limited evidence to evaluate the efficacy and safety of siltuximab on patients with COVID-19. There are no completed clinical trials for Sarilumab at present. More data from ongoing and planned clinical trials are needed to establish the role of IL-6 inhibitors in the management of such patients.

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d. ANTI-TNF or TNF INHIBITORS

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Introduction

TNF-α plays a role in facilitating the entry of the SARS-CoV into the host cell; thus, anti-TNF-α has been considered as a possible early treatment modality to reduce SARSCoV infection, as currently being studied in a randomized controlled trial (RCT) in China.

Mechanism of Action

Decrease of angiotensin converting enzyme 2 (ACE2) expression and an increase in the activity of the renin-angiotensin system facilitate entry of the SARS-CoV into the host cell. The SARS-CoV viral protein promotes shedding of the ACE2 ectodomain through the action of TNFα - dependent converting enzyme. This may also be one of the mechanisms of viral infection in SARS-CoV-2. Inhibition of TNFα may then be an important step in reducing SARS-CoV infection and the concomitant target organ damage.[1]

Adalimumab is a human recombinant mAb directed against the soluble and cellbound forms of tumor necrosis factor alpha (TNF- α).[2]

Clinical Studies

There is an ongoing prospective, single center, phase II trial evaluating the efficacy of infliximab or infliximab-abda in hospitalized adult patients with severe or critical COVID-19.[3]

There is one registered clinical trial on the efficacy and safety of adalimumab for severe COVID-19 pneumonia.

Recommended Dose

In an ongoing trial on infliximab for treatment of severe or critical COVID-19 patients, the dose being given is 5mg/kg/day IV. A second dose of infliximab may be given 7-21 days following the primary therapy.[3]

Adverse Effects

Serious adverse reactions (>0.2 events/100 patient-years) among adults include
cellulitis, pneumonia, appendicitis, herpes zoster and urinary tract infection. Less than 0.2/100PY presented with active tuberculosis infection.[4] In children common adverse reactions include infections such as upper respiratory tract infection,

nasopharyngitis and headache. Pneumonia was identified as the most common serious adverse reaction.[5]

While TNF inhibitors may interfere with viral penetration into the cell, a slight increase in the risk of viral infection is also possible.[1]

Interactions between adalimumab and drugs other than methotrexate have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with methotrexate or commonly used DMARDs (sulfasalazine, hydroxychloroquine, leflunomide and parenteral gold) glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.[6]

Conclusion

There are no completed studies on the use of TNF inhibitors for the treatment of COVID-19. A clinical trial is currently being conducted in the United States.

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e. CCR5 INHIBITOR (LERONLIMAB)

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Introduction

Leronlimab (Pro 140) is an investigational drug primarily studied for HIV infection and recently under Emergency Investigational New Drug (eIND) for COVID-19 by the US FDA.[1]

Mechanism of Action

It belongs to the drug class known as the CCR5 inhibitor or antagonists. C-C chemokine receptor type 5 (CCR5) is a co-receptor of the CD 4 receptor on the surface CD 4 cells. It blocks the entry of some viruses particularly HIV and potentially SARS-CoV-2, preventing its entry into and activation of CD4 cells. Thus, it mitigates the release of inflammatory cytokines such as IL-6 and TNF alpha and the ensuing "cytokine storm".[1]

Clinical Studies

As of April 28, 2020, Leronlimab (Pro 140) a CCR5 antagonist target therapy immunomodulator drug has been approved for 54 patients for eIND with the US FDA. There are 49 patients enrolled in a Phase II and Phase IIb/III randomized double blind trial[2] for mild to moderate and severely and critically ill COVID-19 patients respectively. A eIND for compassionate use was requested for the patients who did not qualify for the trials. The primary clinical end point is on day 28 and secondary endpoint is on day 14.

The preliminary results are from the 14th day clinical end point for severely and critically ill of the Phase IIb/III trials. The initial results provided are from the 39/49 patients enrolled and are awaiting the report of 10 patients . Of the 39 patients, 9 (23%) patients went home, plus 18 (46%) patients showed improvement (including extubation, weaning mechanical ventilation, decreasing need of O2), 2 (5%) remained the same, 3 (8%) patients deteriorated, and 2 (5%) have pending results. So a total 32(82%) patients are still alive, with 69% of patients reported improved or improving and 5% remained the same and 8 percent deteriorated [2].

Recommendad Dose:

700 mg subcutaneous[2]

Adverse Effects

Since Leronlimab is still under study, the present information on its side effects may yet be incomplete. As more trials conducted, information on these adverse reactions will be gathered.[1]

Conclusion

The preliminary results of a Phase IIb/Phase III randomized double blind trial of Leronlimab for severe to critically ill COVID-19 patients seem very promising although the initial data should be interpreted with caution as the study is still ongoing. The results for Leronlimab for mild to moderately ill COVID-19 are not yet available.

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f. INTERLEUKIN 2

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Introduction

Interleukin-2 (IL-2) has been discovered in 1976 as a T cell growth factor. IL-2 is a key cytokine for Treg cell differentiation, survival, and function[1,2,3,4] and induction of antibody production by B cells. This has led to new opportunities for tipping the balance between Treg and effector T cells towards Tregs development.[5]

The immunological and clinical effects of low dose IL-2 have already been observed in the treatment of different autoimmune diseases such as such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriasis, Behcet's disease, granulomatosis with polyangiitis, Takayasu's disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis and sclerosing cholangitis.[6]

Mechanism of Action

Aldesleukin (recombinant IL-2; rIL-2) is a non-glycosylated interleukin-2 (IL-2) product, made via recombinant DNA technology that uses an *E. coli* strain containing an analog of the human IL-2 gene[7] . The biological activity of aldesleukin is similar to that of endogenous IL-2. Aldesleukin is currently FDA-approved for treating metastatic renal cell carcinoma and melanoma.[7] In HIV-related clinical trials, aldesleukin is the most commonly studied IL-2 product.[8]

Low dose IL-2 specifically activates the T reg cells and improves inflammatory conditions arising from T reg insufficiency such as allergy and autoimmunity in mice and humans[9,10,11,12,13]. IL-2 has also been used in the field of transplantation.[9] However, given the pleiotropic effects of IL-2 on other immune cell types that also respond to IL-2 in higher doses, such as CD4 and CD8 effector T cells (Teff), natural killer cells, and group 2 innate lymphoid cells[12] and given its short half-life[14], finding a dose and schedule of administration that can maintain a proper balance of Treg/Teff cells over time is the key to the therapeutic use of low dose IL-2.[15]

Depletion of Treg cells in models of lung infection and after beryllium exposure has been observed to aggravate lung inflammation, thus the important role of Treg during early ARDS and its resolution is clear. Low dose IL-2 is the first therapy during Treg-specific expansion and activation. It was successfully tested in a wide range of preclinical models of inflammatory diseases including beryllium-induced lung inflammation. It was also observed that IL-2 is very low in concentration in the blood and bronchoalveolar lavage supernatant of patients in early phase of ARDS so additional IL-2 could be beneficial for Treg expansion.

This was lifted from a manuscript that describes how IL-2 can be used as treatment for ARDS caused by COVID-19.

Clinical Studies

There is presently an ongoing interventional study in Paris, France on low dose IL-2 in acute respiratory distress syndrome related to COVID-19 patients. Thirty participants will be recruited with the aim of investigating the therapeutic benefit of low dose IL-2 as a Treg inducer for controlling SARS-CoV2 related ARDS.

Recommended Dose

No specific dose was mentioned in the study of IL-2 given to COVID-19 related ARDS.

Adverse Effects

Common adverse effects of Interleukin-2 are fever and flu-like symptoms, generalized flushing of the face and body, nausea and vomiting, lower blood pressure, diarrhea and changes in mental status. These side effects occur in more than 30% of patients, are predictable and reversible when treatment is completed. A serious, but very uncommon side effect of Interleukin-2 in high doses is "capillary leak syndrome" or "vascular leak syndrome." [16]

Conclusion

Interleukin-2 may have beneficial effects in controlling inflammatory lung disease but more studies are needed to verify its effectiveness and efficacy for COVID-19.

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g. JAK 1 & 2 INHIBITORS

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Introduction

JAK 1 and 2 inhibitors currently being studied for the treatment of COVID-19 include baricitinib, ruxolitinib and jacketinib. The use of fedratinib in the treatment of COVID-19 is being proposed. Baricitinib was licensed in 2018 for treating rheumatoid arthritis with excellent clinical response and no significant safety concerns.[1,2,3] Ruxolitinib was licensed for the treatment of myelofibrosis in 2012,[4] polycythemia vera in 2015,[5] and graft-versus-host disease in 2019.[6] Jacketinib is still in its phase II clinical trials for the treatment of myelofibrosis, severe alopecia areata, idiopathic pulmonary fibrosis, rheumatoid arthritis, ankylosing spondylitis, severe plaque psoriasis; and moderate to severe atopic dermatitis.[7] Fedratinib is a newly licensed treatment for myeloproliferative neoplasm-associated myelofibrosis in 2020.[8]

Mechanism of Action

Baricitinib, jacketinib, fedratinib and ruxolitinib are selective inhibitors of Janus kinases (Jaks) 1 and or 2. Janus family of kinases comprises four members: Tyk2, Jak1, Jak2 and Jak3. They associate with cytokine receptors of interleukins, interferons, and colony stimulating factor, as well as classic hormones such as erythropoietin, prolactin and growth hormone. Upon ligand binding, Jaks phosphorylate the cytokine receptors and induce recruitment of other cellular transcription factors which directly initiate gene expression and cytokines production such as interferon alpha, interferon gamma and IL-6. Inhibition of Jaks 1 and 2 by baricitinib blocks the production of these cytokines thereby dampens the inflammatory response by the host.[4,7,8, 9, 10]

Baricitinib also effectively inhibits AP2-associated protein kinase 1 (AAK1) and cyclin-G associated kinase (GAK) which mediate viral endocytosis, thereby inhibits viral entry into the host cells.[9,10]

Knowing the advantageous action of JAK 1 and 2 inhibitors on cytokine outbreak and additional action of baricitinib on viral entry, it has been suggested that they could be used in COVID-19 patients with acute respiratory disease. Their role would be to reduce viral entry and or aberrant inflammatory response in the patients.[11]

Compared to the other JAK inhibitors, baricitinib with its high affinity for AAK1 is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile. In addition, the potential for combination therapy with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. There is the potential for combining baricitinib with the direct acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drug metabolizing enzymes.[12]

Clinical Studies

A non-peer reviewed article on in vitro testing of anti-SARS-CoV-2 activities of several drugs reported that baricitinib showed no inhibitory activities against SARS - CoV-2 at the concentration of 3 μM or 3.2 μM.[13] Three (3) case report studies done in Italy showed successful recoveries in COVID-19 patients who were given baricitinib. Two studies from the ClinicalTrials.gov on baricitinib for COVID-19 have completed the trials. The first study, a non-randomized, open-label, cross-over trial, showed significant improvement clinically of laboratory parameters in the baricitinib group. None of them required ICU support and majority (7/12) were discharged at week 1 and 2 after the start of treatment (p=0.027).[14] In the second study, a retrospective cohort, 12 (73.3%) patients given baricitinib recovered with normal body temperature and decreased inflammatory markers and need for oxygen support. However, 3 (13.3%) patients who were not given baricitinib died due to secondary bacterial or fungal infections during prolonged ICU stays.[15](Appendix 11) Wu D. et al concluded in their reviews that fedratinib can suppress the production of several TH17 signature cytokines, therefore promising to prevent the deteriorating outcomes of TH17 associated cytokine storm in COVID-19.[16]

Fourteen clinical trials of baricitinib, 20 of ruxolitinib and 1 of jacketinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future. (Appendix 12-C)

Recommended Dose

Baricitinib:[17]

Adult dose: 2-4mg once daily for 10-14 days

Pediatric dose: Safety and efficacy not established

Ruxolitinib:[18]

Adult dose: 10mg twice daily for 14 days

Pediatric dose ≤12 y/o: Safety and efficacy not established[12]

Jacketinib:[19]

Adult dose: 50-100mg twice daily for 7 consecutive days

Pediatric dose: Safety and efficacy not established

Fedratinib:[20]

Adult dose: 200-400 mg orally once a day

Pediatric dose: Safety and efficacy not established

Adverse Effects

The majority of adverse reactions of baricitinib are mild, such as upper respiratory tract infections. However, there is a Black Box Warning regarding: (1) Serious and sometimes fatal infections may develop owing to bacterial,

mycobacterial, invasive fungal, viral, or other opportunistic pathogens; (2) Lymphoma and other malignancies observed; (3) Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), observed at an increased incidence.[17] Ruxolitinib and fedratinib, on the other hand are associated with peripheral blood cytopenia, hyperlipidemia and elevated liver enzymes.[17, 20] Ruxolitinib may also cause viral as well as bacterial infections.[18] Wernicke's encephalopathy has occurred in patients treated with fedratinib. Fedratinib should not be started in patients with thiamine deficiency.[20]

Conclusion

There are only 2 clinical trials that concluded the effectiveness and safety of baricitinib in the treatment of COVID 19. Findings of the ongoing studies of JACK 1 and 2 inhibitors will help strengthen their use in this setting.

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