All available clinical data on anakinra in COVID-19: an updated comprehensive review

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Abstract

Background: Based on the investigations, cytokine-release syndrome (CRS) play a key role in the development of acute respiratory distress syndrome (ARDS) following SARS-CoV-2 infection. Anakinra can be effective in the management of CRS by inhibiting IL-1 from binding to the interleukin-1 receptors. We aimed to review the current clinical evidence regarding the therapeutic effects of anakinra in the management of ARDS in the context of the coronavirus disease 2019 (COVID-19). Methods: PubMed and google scholar databases were searched and all of the case reports, case series and RCTs were reviewed. Also, we searched www.clinicaltrial.gov database for ongoing clinical trials of anakinra. Results: Overall, 31 articles were found, and included 9 case report, 6 case-series and 11 RCTs. One of the reports of RCTs was not peer reviewed. Also, ten ongoing studies were found in the clinicaltrial.gov database searching. Conclusion: Four items have been shown to be important to achieve the optimal therapeutic effect of anakinra in patients withCOVID-19. These items include duration of treatment [?] 10 days, doses of more than 100 mg, intravenous administration and early initiation of therapy. Also, the use of corticosteroids in combination with anakinra appears to improve clinical outcome compared to monotherapy with anakinra.

Article type: Review article

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Methods: PubMed and google scholar databases were searched and all of the case reports, case series and RCTs were reviewed. Also, we searched www.clinicaltrial.gov database for ongoing clinical trials of anakinra.

Results: Overall, 31 articles were found, and included 9 case report, 6 case-series and 11 RCTs. One of the reports of RCTs was not peer reviewed. Also, ten ongoing studies were found in the clinicaltrial.gov database searching.

Conclusion: Four items have been shown to be important to achieve the optimal therapeutic effect of anakinra in patients with COVID-19. These items include duration of treatment ≥ 10 days, doses of more than 100 mg, intravenous administration and early initiation of therapy. Also, the use of corticosteroids in combination with anakinra appears to improve clinical outcome compared to monotherapy with anakinra.

Keywords: anakinra; COVID-19 treatment; cytokine-release syndrome; novel coronavirus disease 2019; acute respiratory distress syndrome.

Introduction

Based on reports from World Health Organization (WHO) the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected more than 135 million patients, resulting in more than 2.92 million deaths worldwide up to April 9, 2021. Patients with COVID-19 have a wide range of symptoms with variable severity (1). Acute respiratory distress syndrome (ARDS) is the most overwhelming complication of COVID-19, with a high rate of mortality. It has been shown that, cytokine-release syndrome (CRS) has a key role in the progression of SARS-CoV-2-induced ARDS. The hyper-inflammatory state in patients with COVID-19 resembles the CRS in Hemophagocytic Lymphohistiocytosis (HLH), macrophage activation syndrome, or chimeric antigen receptor T-cell therapy. All these conditions are associated with very high levels of serum pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 18 (IL-18), and interferon γ that leads to uncontrolled, self-sustaining multi-organ damage. Cytokine-blocking medications such as anakinra are potent treatment options for these conditions. SARS-CoV-2 can trigger the immune response of infected patients that leads to hyperinflammation, cytokine storm, tissue injury especially in the lungs, and eventually death (2–6). Furthermore, COVID-19-induced CRS could result in impaired viral clearance, reduced levels of type I interferons and increased neutrophil extracellular traps (NETs) (7). Despite the important role of the proinflammatory phase in the pathogenicity of SARS-CoV-2, currently there is no approved immunomodulator therapy for the management of the severe disease. Unlike most of the inflammatory factors that increase after progression of respiratory dysfunction, the elevation of IL-1 level occurs before disease progression, which magnifies the role of IL-1 in severe COVID-19 and ARDS pathogenesis. IL-1 is a proinflammatory cytokine that is produced preliminary from phagocytic cells and activated B and T lymphocytes. Moreover,

liver, pancreas, bone, muscle, fibroblasts, and brain are affected by IL-1. IL-1 can stimulate the thermoregulatory center in the brain that causes fever in patients (8,9). Overall, there are two types of IL-1, IL-1α, and IL-1β which are produced by different types of cells. Dying Epithelial and endothelial cells could produce IL-1α and infiltrating monocytes, macrophages, and neutrophils could produce IL-1β. Active and mature IL-1β is one of the main factors in the acute phase of hyperinflammation and cytokine storm syndrome, which can cause tissue injury and severe illnesses in COVID-19 patients. SARS-CoV-2 can activate the inflammasome from binding to the toll-like receptor , which results in the production of active and mature IL-1β by caspase (10).

Based on the pathogenesis of COVID-19, IL-1 inhibitors might be one of the potential treatment options for COVID-19 patients who show symptoms of hyperinflammation and cytokine storm syndrome. Anakinra is the first biologic (recombinant) drug that acts as an IL-1 receptor antagonist, which can inhibit IL-1α and IL-1β. Anakinra has a short half-life and is administered by subcutaneous and intravenous injections. Anakinra is commonly used in macrophage activation syndrome caused by various inflammatory conditions like rheumatoid arthritis. Short half-life of anakinra could be either beneficial or problematic; while discontinuation of the drug could result in its rapid clearance and could be useful in case of an adverse effect specially in critically ill patients, it could result in large peak and trough fluctuation with the intravenous administration. Anakinra has been shown to have good efficacy, safety, and tolerability in inflammatory disease other thank COVID-19 and is under investigation for the treatment of SARS-COV-2 infection (11–13). Due to the known beneficial effects of anakinra in the treatment of CRS and the pivotal role of IL-1 in SARS-CoV-2-induced CRS, we aimed to conduct a systematic review regarding the use of anakinra in patients with COVID-19.

Method

For the purpose of organizing this systematic review, the PubMed database was searched from the beginning of December 1, 2019 till April 30, 2021, using following keywords:

((COVID-19) AND (anakinra [Title]) AND (clinical improvement OR good outcome OR lower mortality OR decrease admission to ICU OR avoid mechanical ventilation OR improvement in respiratory function OR change in inflammatory biomarkers))

Also, google scholar was searched for articles containing keywords anakinra and COVID-19 in their title or abstract.

The articles were screened for duplication by 2 investigators. Due to the novelty of the subject and lack of related studies, different study types as case studies, case series, and randomized clinical trials (RCTs) were selected for reviewing. The full texts of articles were read and the results are written. Finally, the manuscript was edited and reviewed by two other investigators.

Results

Overall, 31 articles were found about using anakinra alone or in combination with other drugs in COVID-19 patients, which consisted of 9 case report, 6 case-series and 11 RCTs. Further data about the dose of anakinra and concomitant or prior treatments before anakinra initiation are mentioned in three tables. Most of the studies conclude that the anakinra could be effective for the treatment of COVID-19 patients with special features indicating sever disease. Also, the trials which are ongoing or completed but their results were not available were mentioned in Table 4, Table 5, and Table 6.

Case reports

Further data on case reports are provided in Table 1

1. This was first case of severe, RT-PCR (Reverse transcription polymerase chain reaction) test confirmed COVID-19 with bilateral ground glass opacities on chest CT (computed tomography) scan, who was treated with anakinra(14). A 50-year-old man was presented to the hospital with the history of fever and dyspnea. Initially, the patient was managed with lopinavir/ritonavir, hydroxychloroquine and non-invasive ventilation. Due to the reduction of respiratory function in the following 3 days, the patient was admitted to the ICU and put on mechanical ventilation. At the time of admission to the ICU the following findings were recorded: PaO2:FiO2 (arterial oxygen partial pressure to fractional inspired oxygen)160; PEEP=12 cm H2O and FiO2 50%. Based on the liver enzymes level which was 5 times more than upper limit(5×ULN), remdesivir and tocilizumab were considered contraindicated. At day 10 his respiratory function was worsened with the following findings recorded: PaO2/FiO2=85, PEEP=14, and FiO2=50% and hyperinflammation was diagnosed by high level of ferritin (>3000 ng/ml). Therefore, anakinra was ordered for him on day 10 of admission intravenously, followed by 100 mg 4 times daily subcutaneously. After starting anakinra, antiviral therapy and immunosuppressives or immunomodulators were interrupted. 72 hours after starting anakinra, inflammatory markers including lymphocyte count, and liver enzymes were significantly reduced. Also, respiratory improvement was evident (PaO2/FiO2 270; PEEP 10; FiO2 30%). Eight days following initiation of anakinra (day18), he was discharged from ICU. Four days later, his body temperature was increased and because of sustained good respiratory function, it was assumed that the reason of fever was central venous catheter-related bacteremia. Therefore, anakinra was interrupted and empiric antibiotics were started after removing intravenous catheter. Eventually, the patient was

discharged from the hospital on day 29. The patient received anakinra for a total duration of 15 days.

2. A 33-year-old man with history of progressive retrosternal chest pain for 5 days was referred to the emergency department with low back pain which was since 7days before admission (15). Laboratory examinations revealed high levels of troponin T and CRP (C reactive protein) (<5 ng/L and 73.8 mg/dl, normal<5), normal levels of D-dimer, IL-6 (0.26 ng/mL and 43.6 pg/mL), and lymphopenia (1060/mm3). His COVID-19 infection was confirmed by positive result of RT-PCR. Treatment protocol for COVID-19 included hydroxychloroquine and moxifloxacin (dosing was not specified by the authors) with analgesics. After three days, there was not any improvements in pain and level of D-dimer was elevated. The chest CT-scan has showed minimal changes including ground-glass opacification, subpleural curvilinear lines, and pericardial effusion, but no signs of pulmonary thromboembolism was evident, therefore enoxaparin was started with a dose of 40 mg twice daily due to the elevation of D-dimer level. Five days after admission, pericarditis was confirmed by clinical manifestation, laboratory assay and electrocardiogram (ECG) findings so colchicine was started. Five days after initiation of treatment, inflammatory markers raised again and patient's clinical status worsened. Therefore, anakinra was ordered for 7 days. The chest pain was controlled rapidly and levels of inflammatory markers like CRP and D-dimer were normalized 7 days after starting anakinra. In brief, this was a case of COVID-19 infection and refractory pericarditis which was treated successfully with anakinra.

3. A 53-year-old female was presented with a history of cough, fever (>38°C), and dyspnea of 4 days duration (16). The patient's history was indicative of asymptomatic non-progressing meningeal tumor, type 2 diabetes, arterial hypertension, hepatic stenosis, and psychiatric

borderline syndrome. Drug history included metformin and antihypertensive medications which were not specified by the authors.

At the time of admission, her physical examinations showed a respiratory rate of 22 breaths/min and body temperature of 38.9°C, severe bilateral infiltration in the upper and lower lobes of lungs were shown in chest x-ray and laboratory results revealed a CRP level of 242 mg/dL, a D-dimer level of 0.66 mg/dL, and mild lymphopenia.

Rapid nucleic acid amplification test (NAAT) for SARS-COV-2 RNA was positive and because of lack of effective therapeutic option, hydroxychloroquine was started on day one and continued until day 5, at which time it was interrupted due to drug-induced long QT syndrome. Two days after stopping hydroxychloroquine her body temperature was elevated to 40°C, therefore anakinra was initiated on day 7. The treatment with anakinra was interrupted on days 12 and 13 and was restarted on day 14. Overall, she received anakinra from day7 to day 18 for 9 days (9 doses). Following receipt of anakinra the patient's body temperature and levels of inflammatory biomarkers decreased and respiratory function improved.

On day 19 the patient's mean arterial pressure was lower than 60 mmHg and she required supplemental oxygen because of dyspnea. These signs were in correlation with sepsis so meropenem and ciprofloxacin were initiated empirically. On day 22 CRP and procalcitonin levels were elevated to 411 mg/dL and 208 ng/mL respectively, and based on the results of antibiogram, ciprofloxacin was continued for the patient. After 5 days, a tracheostomy was performed. In the following days, the patient was able to breathe without mechanical support therefore she was transferred to the rehabilitation center. The authors concluded that immunomodulators like anakinra could be an effective therapeutic option in COVID-19 infected patients with signs of hyperinflammatory syndrome and ARDS, however, they added

that immune system dysfunction following anakinra administration might postpone the viral clearance and increase the risk of bacterial superinfection and sepsis (17).

4. A 50-year-old man with a body mass index of 30 kg/m^2 that has a medical history for renal stones, cholecystitis, was admitted to the hospital with a history of sore throat for 7 days, fever for 5 days and difficulty in breathing for 2 days before presentation (18). other symptoms at the time of admission included fever and tachycardia. His oxygen saturation was 90% and the signs of type1 respiratory failure were observed. Laboratory results of this patient on the day of admission were as follows: WBC (white blood cell) 14.38×10^9/L, lymphocytes 1.72×10^9/L, procalcitonin (PCT) 0.99 ng/ml, and CRP 358 mg/L. The diagnosis of SARS-COV-2 infection was confirmed by RT-PCR and chest X-ray results, which showed bilateral Suprahilar patchy reticulonodular opacities with shadowing. Due to the COVID-19 pneumonia with superadded infection, the patients received Amoxicillin and clavulanate and supportive therapy with supplemental oxygen. On the following days, his inflammatory markers and oxygen requirement increased and fever persisted. Also, extensive ground-glass opacification bilaterally and dense consolidation on both lower lobes were identified in patient's CTPA (computer tomography pulmonary angiogram) but no central pulmonary embolism was seen so the patient was admitted to the ICU a for ventilation on day 6 of hospitalization. The patient's clinical condition was deteriorated later in the course of hospitalization with fast atrial fibrillation and hypotension. Laboratory examinations revealed multiple disturbances including WBC=23×10^9/L, lymphocytes=1.17×10^9/L, CRP=448mg/L, PCT=3.56 ng/mL, troponin=3965 ng/L, and lactate 2.7 mmol/L. Based on creatinine level (268 μmol/L showing acute kidney injury) the patient required hemofiltration. Echocardiography revealed some abnormalities including dilated right ventricle (RV), preserved RV function, global left

ventricular hypokinesia, and severe left ventricular systolic dysfunction (ejection fraction 35%-40%), in accordance with myocarditis but acute coronary syndrome could not be excluded so dual antiplatelet therapy and unfractionated heparin were started in order to ensure full anticoagulation. On day 9 his inflammatory markers were increased (ferritin 85 789 μg/L, and CRP 338 mg/L). So, he was considered to be in a cytokine storm and high dose intravenous anakinra was begun for 7 days. After starting treatment, the need for supplemental oxygen, level of ferritin, and CRP were significantly reduced, the patient was not feverish at days 2 and 7 following anakinra initiation and oxygen saturation improved (93% on a FiO2 of 0.25).

After 3 weeks, due to evidence of improvement in patient's chest X-ray, the physicians decided to extubate the patient, but he died on day 21 because of sagittal sinus thrombus and brain injury. The PT (Prothrombin time) and PTT (partial thromboplastin time) of the case were not reported in the article but thromboembolism occurred while the patient was receiving full dose of heparin. So, there is a possibility that anakinra somehow could have contributed to the development of this complication.

5. A 48-year-old man with a medical history of intermittent atrial fibrillation and hypertension was admitted to the hospital 8 days after symptoms onset because of dyspnea (19). His baseline laboratory results reported first-grade leukopenia, high levels of CRP (10.5 mg/dL), and LDH (311 U/L). The patient's RT-PCR test was positive for SARS-COV-2 infection.

In the latter days the levels of CRP, LDH and ferritin increased (49mg/dL, >737U/L and 26252 microg/L). At this time the level of IL-6 was 211 pg/mL. Based on this level of biomarkers grade 4 cytokine storm syndrome was diagnosed.

On day 14, following symptoms initiation, anakinra was started control cytokine storm syndrome.

Three days after start of anakinra Lactate Dehydrogenase (LDH), IL-6, and ferritin were significantly decreased and ferritin was stabilized after 1 week. One day after termination of treatment with anakinra, control of cytokine storm syndrome was evident and the patient was extubated.

While anakinra and tocilizumab have a similar rationale of use, anakinra was preferred to tocilizumab by the authors of this report because of its shorter half-life and milder long-term immunosuppression that leads to lower rates of secondary infections and other side effects compared to tocilizumab, and evidence showing that anakinra is more effective in autoinflammatory conditions.

6. A 62-year-old woman with a medical history of primary progressive multiple sclerosis was admitted due to symptoms including acute alerted level of consciousness, hypoxemia, shock, respiratory rate of 32 breaths/min, and oxygen saturation of 95% on 100% oxygen by a non-rebreather face mask (20). Her blood pressure and heart rate were 55/32 mmHg and 120beats/min respectively. Her laboratory results showed elevated levels of inflammatory biomarkers (ferritin 3067 U/L, CRP 68.2 mg/L, D-dimer 6920 ng/mL, LDH 1094 U/L, and creatinine 2.82 mg/L). RT-PCR positive with dense airspace opacities in the right lung and ground-glass opacities in the left lung as shown by CT scan, confirmed the SARS-COV-2 infection. Although the blood culture was negative on day 0 but following treatments were started; boluses of intravenous fluids, one dose of intravenous dexamethasone and full course of ceftriaxone and azithromycin. Some abnormalities were shown on ECG including sinus tachycardia with diffuse anterolateral ST-elevation and highly sensitive cardiac troponin T was 4986 ng/L. Also, cardiac magnetic resonance imaging showed fulminant acute myocarditis with severe left ventricular dysfunction (LVEF 24%), therefore anakinra was ordered with a

dose of 100 mg twice daily intravenously for 5 days. After 72 hours, significant reduction in heart rate and inflammatory markers and clinical improvements including, oxygen requirement, and blood pressure was observed. Fourteen days after initiation of anakinra, the Cardiac magnetic resonance (CMR) imaging demonstrated left ventricular ejection fraction elevated to 54%, LGE signal intensity was reduced and global reductions in myocardial T1 and T2 values and extracellular volume were seen. Also, pulmonary consolidation and pleural effusions were improved. This was the first case of fulminant myocarditis in context of COVID-19 managed by anakinra and dexamethasone who was successfully discharged from the hospital. It should be noted that dexamethasone, due to its anti-inflammatory and beneficial effects in COVID-19 patients, may have accelerated rapid clinical improvement in this case making it difficult to yield a firm conclusion about the effects of anakinra.

7. Multisystem inflammatory syndrome (MIS) is recently recognized as a late complication of COVID-19 in pediatric patients (21). The characteristic and treatment strategy of this condition is similar to those of the Kawasaki disease, streptococcal / Staphylococcal toxic shock syndrome, and Sepsis (22,23). The case was presented to the hospital with chief complaint of fever and SARS-CoV-2 infection was confirmed by RT-PCR after ruling out other etiologies. Although the patient did not show any respiratory symptoms and her oxygen saturation was normal, her chest x-ray showed bilateral infiltration which confirmed the SARS-COV-2 infection.

At the time of admission, her laboratory results revealed lymphocytic leukocytosis, normochromic normocytic anemia, thrombocytopenia, hyponatremia, hypoalbuminemia, high level of hemoglobin and lactic acid, her kidney function was normal, ASpartate amino Transferase (AST) and Alanine Transaminase (ALT) level had mild growth and her CRP level

was increasing continuously. Also, her examinations have showed mild hepatosplenomegaly but no skin rash, lymph nodes enlargement or any sign of Kawasaki disease were present.

Her RT-PCR tests for SARS-CoV2 and other respiratory viruses were negative on days 2, 8 and 9, but the patient remained febrile with elevated heart rate and inflammatory markers like CRP, troponin, ferritin and Natriuretic peptide.

Packed red blood cells were infused and Intravenous Immunoglobulin (IVIG) with aspirin and single dose of dexamethasone were given. Also, pulse of corticosteroid was ordered for 3days. After this treatment the level of inflammatory markers were still high, therefore anakinra was given for 9 days as second line immunomodulatory agent because of its known efficacy and safety in similar conditions. Anakinra was started at day 17 following illness onset. During treatment with anakinra, antibiotics (piperacillin/tazobactam) were continued. At day 34 of admission and 24 hours after anakinra discontinuation, recurrence of fever observed and the managing team opted to give the patient a second dose of IVIG. After staying at hospital for 5 weeks, the patient was discharged. This report brings up a role for anakinra in treatment of pediatric patients with severe MIS unresponsive to routine therapeutic options.

8. This was another case of MIS which has been reported in many pediatric COVID-19 patients (24). The syndrome has similar features to classical Kawasaki disease and Kawasaki shock syndrome including respiratory and gastrointestinal symptoms and cardiac involvement (typically with myocarditis and shock) which results in severe form of COVID-19 infection.

The possible hypothesis is that response of immune system to the coronavirus could cause hyperinflammation and eventually cytokine storm which followed by MIS in pediatric patients. However it is a not common complication of COVID-19 infection(25)

Case 1: A 3-year-old girl was presented to the hospital with high fever, abdominal pain and diarrhea of two-days duration. RT-PCR test was performed and it was positive for SARS-COV-2 but chest x-ray was normal. Skin rash, bulbar non-exudative conjunctivitis, palmar hands edema and cheilitis were present at admission. Laboratory results revealed thrombocytopenia, severe lymphopenia, and hypofibrinogenemia, high level of CRP (145 mg/L) and PT ratio (INR 1.7), D-dimer (4 mg/L), increasing level of cytokines, IL-1Ra 10468 pg/mL, IL-6 177 pg/mL, IL-10 363 pg/mL, IP10 (IFN-inducible protein-10) 17795 pg/mL, G-CSF (granulocyte colony-stimulating factor) 657 pg/mL, and MCPI (monocyte chemoattractant protein 1) 299 pg/mL. Immunological assays did not show any alteration.

Treatment with IVIG and intravenous methylprednisolone were initiated but patient indicated poor response with these modalities. Therefore, continuous infusion of anakinra was initiated for the patient. Anakinra was ordered based information available on dosing in MAS (Macrophage activation syndrome) in pediatric patients (12 mg/kg/day) (26). Low molecular weight heparin (LMWH) and fibrinogen were also added to the anakinra.

Clinical improvement occurred two days after receiving anakinra, at which time noninvasive ventilation was stopped and CRP levels decreased. Total duration of treatment with full dose anakinra was 8 days, after that, its dose was tapered and patient was discharged from the hospital with normal clinical condition.

Case 2: A 10-year-old girl was presented to the hospital with high fever, vomiting, headache, abdominal pain, maculopapular skin rash and bilateral cervical lymphadenopathy for 5 days. Before admission patient had received empiric antibiotic with no observable response. Laboratory results revealed lymphopenia, thrombocytopenia and high levels of inflammatory markers (CRP 272 mg/L, ESR 64 mm/h, and ferritin 560 mcg/L) and cytokines (IL-1Ra 1,854

pg/mL, IL-6 59 pg/mL, IP10 11,337 pg/mL). Immunological work up did not show any abnormalities.

Methylprednisolone and IVIG were started with no meaningful clinical or biological response observe. Subsequently subcutaneous anakinra was initiated in combination with LMWH. In less than 24 hours after receiving anakinra, patient was defervesced; although clinical and biological conditions improved quickly, fibrinogen levels took longer to lower. Anakinra was tapered during 10 days and stopped.

Based on the existing evidences, COVID-19 infection related MIS is a delayed inflammatory response to prior infection (27) so the virus assay could be negative and the authors of these cases justified the use of anakinra in case 2, with negative RT-PCR test, by referring to this evidence. They also referred to results of a study that demonstrated beneficial effects with the use of anakinra in combination with glucocorticoids in patients with severe forms of COVID-19 (28) to explain the logic behind continuing methylprednisolone after anakinra initiation.

Both of the cases had good response to the anakinra treatment, their clinical conditions improved, laboratory values normalized and no adverse event were reported. Despite the promising effect of anakinra in COVID-19 related MIS, it is used in patients with severe cardiological involvement and as second line treatment in patient who had poor response to combination of glucocorticoid and IVIG. Due to the important role of IL-1 in the pathogenesis of inflammatory cardiac disease and pericarditis, anakinra can be very effective in idiopathic pericarditis or other cardiac injury (29,30).

The authors concluded that due to poor responses to combination of glucocorticoid and IVIG and occurrence of cardiac involvement in pediatric COVID-19 patients and considering the observed rapid promising response with anakinra, anakinra should be the first line treatment

in MIS due to the cytokine storm in context of SARS-CoV2 infection which most of the time is seen in the pediatric COVID-19 patients.

Case series

Complementary data on case reports have showed in Table 2

1. A series of 5 patients received high dose of IV anakinra in addition to the standard of care (SOC) which included methylprednisolone in one patient. These patients presented to the hospital with moderate to severe COVID-19 with recent history of fever, dyspnea, systemic inflammation and evidence of abnormalities in chest CT scan (31).

Use of anakinra in this situation was based on the results of previous studies that demonstrated beneficial effect of this agent in management of complications because of massive cytokine release.

Anakinra was ordered intravenously for 1 or 2 days, followed by gradual dose decrease adjusted to patient's response. Based on the Berlin criteria (32) and PaO2:FiO2, none of the reported patients were categorized as being in severe ARDS and only 2 of the patients had CRP levels higher than 10 mg/dL.

The main limitations which could have affected the reported results of this article included small number of sample size, short duration of receiving anakinra and diversity of laboratory results in patients.

No inclusion or exclusion criteria was defined for the patients evaluated in this study. However, all patients were successfully treated with high-dose intravenous anakinra and discharged from hospital between 6 to 13 days after initiating the medication. Anakinra was started on average 1.4 days after admission and it safely and effectively controlled the presentations of cytokine release syndrome.

2. In this case series, nine patients with age ≥ 18 and moderate to severe COVID-19 who were hospitalized in non-intensive care setting and had oxygen flow requirement of 6 ≤ L/min and CRP levels of ≥ 50mg/L were evaluated (33). The COVID-19 infection was confirmed by positive RT-PCR test and chest CT scan in all cases.

Treatment with anakinra was interrupted after first dose in one case due to acute respiratory failure and ICU admission. Fever controlled after 3doses of anakinra in all remaining cases. Also, clinical and laboratory improvement were observed. CRP level decreased steadily in all patients at day 6 but on day 11 only 5 patients had normal level of CRP. Chest CT scan was performed on days 5 and 8 and no evidence of progression reported.

Patients had symptoms for 4-12 days (mean=8) before receiving anakinra and prolonged duration of symptoms could have limited response to treatment in these cases.

The authors concluded that anakinra could effectively block the upstream inflammatory processes and inhibit cytokine storm even if no exhibitive decreased in CRP levels could be noticed.

3. In this retrospective case series (33), COVID-19 patients with ferritin levels higher 1000 ng/ml plus high level of another biomarkers indicating presence of hyperinflammation and acute hypoxic respiratory failure who required either 15 liters of supplemental oxygen via a nonrebreather mask or 6-liter by nasal cannula or ≥95% oxygen by high-flow nasal cannula were included. No patient who required mechanical ventilation was evaluated in this study.

The dose of anakinra was tapered if a decrease in need for supplemental oxygen and improvement in clinical condition of patients was observed, or adverse effects including increased transaminase levels, cytopenia, or progression in renal impairment occurred, or in case of suspicion to bacterial infection due to positive cultures or increased levels of

procalcitonin to more than 0.6 ng/ml or detection of clinical sign of infection. The maximum duration of treatment with anakinra in these series was 20 days. According to the treatment protocol, the physician's approach was continuing treatment after discharging the patients based on the clinical response and tolerability. Anakinra was discontinued in most of the patients at the time of discharge because the clinical condition of patients significantly improved and relapse of the inflammation was deemed not likely, although it should be mentioned that one patient received anakinra in outpatient setting. In these series of patients, treatment was continued in patients who required mechanical ventilation with the goal of patient's extubation.

Eleven patients received anakinra in this article of whom the first 2 patients received lower than protocol defined doses due to lack of secure supply and consistency of the protocol. Patients who received anakinra within the first 36 hours of fulfilling inclusion criteria for hypoxic respiratory failure (early initiation) did not require intubation or reintubation. But patients who received anakinra 4 days after fulfilling inclusion criteria for acute hypoxic respiratory failure (late initiation) required mechanical ventilation. Anakinra was continued in late-initiation group because of its possible beneficial effects which could lead to patient's extubation. In latter group, two patients developed infection that lead to discontinuation of anakinra, considering that anakinra could enhance the risk of acquiring infection.

The baseline levels of ferritin and CRP were high in all patients (>100 ng/ml and >5 mg/dl). Following treatment with anakinra CRP levels decreased in all but one patient (who developed infection), and levels of ferritin remained lower than 500 ng/ml in only 2 patients after receiving anakinra. At base line lymphocyte count was lower than 1200 cells/μl in 7 patients and 5 patients had lymphocyte count of more than 1500 cells/μl after receiving anakinra.

Six patients received methylprednisolone prior to anakinra and 2 patients received concomitant methylprednisolone with anakinra. The levels of AST or ALT increased in 2 patients during treatment with anakinra and 3 patients developed bacterial infections. One patient who developed bacterial infection after receiving anakinra died after discontinuation of the drug. Injection site reactions occurred in only one patient received anakinra for longest duration.

The authors of this case series concluded that early initiation of anakinra, defined as initiation of the medication <2 days after developing acute respiratory failure, could be effective in COVID-19 patients with evidence of cytokine storm syndrome and could lead to avoidance of mechanical ventilation and facilitation of hospital discharge. But concerns emerge as in patients who were on mechanical ventilation, continuing anakinra might lead to development of bacterial infections.

4. In this study 8 patients with positive Hscore (34), of whom 7 patients were admitted to the ICU and one to the ward, received anakinra (35). Hscore contain 9 variables, the score of all eligible patients were equal or more than 169 which had 93% sensitivity for identification of hemophagocytic lymphohistocytosis (HLH). Detected complications of secondary HLH included pancytopenia, hyper-coagulation, acute kidney injury (only in one patient), and hepatobiliary dysfunction. The main severe complication in these patients were coronary heart disease and arterial hypertension.

The PaO2:FiO2 ratio was lower than 100 in all patients, and all of them were categorized as having severe ARDS. Chest x-ray imaging showed lung infiltrations in all patients.

All patients received hydroxychloroquine and various antibiotics in combination with anakinra but only three patients received concomitant hydrocortisone. Seven out of eight patients received anakinra after intubation. Laboratory parameter improved along day 5 of treatment.

The PaO2:FiO2 ratio was very important because it shown respiratory function, it was significantly increased by end of the treatment in 5 patients and 2 days after that in two patents. Also, Hscore was decreased by the end of the treatment course. Three patients died during 28day study duration, main reason of death was refractory shock and one of the deceased patients developed resistant infection (*Acinetobacter baumannii*) of the central vein catheter.

In conclusion this study showed that anakinra may be effective for COVID-19 patients with sHLH, but risk of serious bacterial infections cannot be ignored.

5. Four patients with severe COVID-19 and focal reactive hyperplasia of pneumocytes, patchy inflammatory cellular infiltration, intracellular thrombosis, high levels of CRP ,and ferritin (between 4000-30000 mg/l) considered consistent with hyperinflammation, were reported in this series (36).

All patients had baseline disease and received immunosuppressants (Sirolimus, Tacrolimus, Rituximab, Prednisolone). SARS-COV-2 infection was confirmed by nasopharyngeal swab examination and chest X-ray. The baseline ferritin and CRP levels were high (range: 2890-40069 and 92-339 respectively) baseline laboratory results were ferritin 24617,4054, 40069, 2890 µg/l; CRP 92, 84, 109, 339 mg/l. Because of high levels of inflammatory markers and severe clinical and respiratory condition anakinra was initiated for the patients. One to two days after receiving anakinra inflammatory biomarkers and creatinine levels decreased and respiratory functions improved. Three of the patients were discharge from hospital between 12 to 24 days after admission. but one patient, who was intubated before receiving anakinra, remained intubated despite decreased levels of inflammatory biomarkers.

All patients who were described in this series, were immunosuppressed and intravenous anakinra was effective for treatment of hyperinflammation in the context of COVID-19

infection. Intravenous anakinra results in drug concentration 24 to 29 times compared to subcutaneous administration. Also, terminal half-life is shorter when used intravenously compared to SC administration (37,38). The authors concluded that anakinra might only be useful in the management of hyperinflammation and not HLH.

6. Thirty-six patients with hematologic malignancies and COVID-19 were admitted to the hospital due to need for oxygen supplementation (39). According to the hospital protocol the first line treatment was hydroxychloroquine in combination with lopinavir/ritonavir. In patients who had high levels of inflammatory biomarkers or who did not show positive response to the HCQ plus lopinavir/ritonavir, corticosteroid and TCZ (tocilizumab)were added. If any improvement was not evident, anakinra was ordered for 5 days.

Five patients with hematological malignancies and indicators of CRS/MAS who failed to respond to tocilizumab, received anakinra. Also, chest X-ray and CT- scan have showed bilateral pneumonia and diffuse ground glass opacities and due to FiO2≥ 40% all patients need to oxygen supplementation without mechanical ventilation. Median duration of symptom onset before admitting to the hospital was 4 days (IQR1-8). All of the patients received first and second-line treatment and any improvement were not occurred. Also, all of them have received single dose of TCZ which was administered intravenously and they were received it between day 5 to 25 after symptom onset. due to lack of response to the treatments and oxygen requirement and inflammatory biomarkers have increased progressively, anakinra was started for patients for 5 days, initiating the treatment with anakinra occurred 5 days after receiving TCZ. Eventually, all of the patients have died from the median 6 (range 1-29 days) after starting anakinra. The reason of death was not clarified in the article. More over any patients had not

received thromboprophylaxis and receiving hydroxychloroquine could increase mortality rate. Also, patients have received low dose anakinra which might not effective in these patients.

RCTs

Further data on cohort studies provide in Table 3

1. This prospective cohort study (40) was conducted in patients who were admitted to the Groupe Hopitalier Paris and have had following criteria: age >18; severe COVID-19 defined as bilateral pneumonia; SARS-COV-2 infection was confirmed by positive RT-PCR or presence of typical findings on CT scan of the chest defined as multiple ground-glass opacities with crazy paving; lack of lymphadenopathy and presence of pulmonary nodules; chest x-ray or CT scan showed bilateral lung infiltration; critical pulmonary function defined as oxygen saturation of ≤93% while receiving ≥6 L/min of oxygen, oxygen saturation of <93% on 3 L/min with a saturation on ambient air decreasing by 3% in the preceding 24 hours. Patients who did not consent to take part in the study, were admitted to ICU, been near end of the life, or had other problems that could have caused respiratory failure were excluded. The intervention group (n=52) who received anakinra was compared with historical SOC group (n=44). Anakinra was administered subcutaneously and dosing was decreased after 3 days. Patient with reduced renal function were also involved in this study. Dose adjustment (100 mg daily for 3 days continued by 100 mg every other day for 7 days) was done for patients who were under dialysis or had glomerular filtration rate less than 30 mL/min. Hydroxychloroquine and azithromycin were administered orally, intravenous ceftriaxone 1g daily or intravenous amoxicillin 3 g daily for 7 days if they didn't have contraindication, and thromboembolic prophylaxis (was not specified by the authors) was also administered. Two patients in intervention group who received pulse dose of methylprednisolone in combination with

anakinra excluded in final analysis. Following supportive care was used for patients: low-flow oxygen therapy defined as ≤6 L/min through low-flow nasal cannula or high-flow oxygen therapy defined as >6 L/min with high-flow nasal cannula or face mask. The group did not have invasive or non-invasive mechanical ventilation at the time of admission to the study. The body mass indexes of historical group were significantly higher in compared to the anakinra group (p=0.0009) which could contribute to increase rate of death in historical group. In comparing two groups about baseline laboratory results showed that platelet counts (Mean= 259×109 vs 201×109 cell/L; p=0.0071) group were significantly higher than historical group. Also, the baseline CRP (173 mg/L) and ferritin (2025 µg/L) level were high.

There were many significant differences between two groups, including longer duration of symptoms before inclusion (Absolute different of mean 2.2 days [0.6 to 3.9]; p=0.0088), and higher percentage of patients who received HCQ (29% [12 to 45]; p=0.0007) and azithromycin (17% [3 to 32]; p=0.015) in anakinra group compared with historical controls. But combined outcomes of need for mechanical ventilation or death [13 (25%) of 52 vs 32 (73%) of 44; (HR 0.22 [95% CI 0.11–0.41; p<0.0001)], death alone (HR 0.30 [95% CI 0.12–0.71]; p=0.0063) and need for invasive mechanical ventilation alone (0.22 [0.09–0.56]; p=0.0015) were higher in historical SOC group.

In this study, 39 out of 55 patients in anakinra group remained alive and didn't need mechanical ventilation. The supplemental oxygen requirements decreased from day 0 to day 7 (median of 7 L/min (IQR 6–9) at day 0 and 2 L/min (0–4) at day 7). Accordingly, the median difference was – 4 L/min (IQR 0–4; p<0.0001, signed-rank test). Based on reported data, before starting treatment with anakinra (day -4 to day 0) CRP level was significantly increased. This level

Immediately decreased after starting the treatment with anakinra during the first 4 days. It was significantly different in comparison to SOC group at the same time.

No difference observed in occurrence of adverse events including increase in liver enzymes, thromboembolic events or bacteriaemia and premature interruption of the treatment between two groups. The authors of this research mentioned that due to lack of randomized control trial, optimal timing and selection criteria for using anakinra in COVID-19 treatment could not be clarifies. Therefore, anakinra may not be useful for majority of COVID-19 patients who have symptoms like influenza-syndrome, but use of IL-1 inhibitor seems to be effective in HLH and CAR T-cell-mediated cytokine release syndrome (26,41). The authors did not clarify the reason of anakinra discontinuation in patients who did so and the levels of IL-1 was not measured which could have caused bias in conclusion.

Overall, the main findings of this study included significant decrease in CRP levels and lower need for mechanical ventilation or death (HR 0.22 [95% CI 0.10–0.49]; p=0.0002) with anakinra. The patients in historical group were more obese compared to anakinra group and based on available information, obesity is considered one of the risk factors of sever COVID-19 and death, therefore this between group difference could have caused biased in results of the trial (42). Anyway, the authors of the study mentioned that although complete ruling out the effects of comorbidities might not have been possible, multivariate analysis resulted in similar outcomes in obese and non-obese patients and patients with confounding factors. The investigators also mentioned that reported data cannot show the effect of anakinra on coagulopathy in context of COVID-19, but other studies have demonstrated that IL-1 increases the level of tissue factor, which is the main factor for coagulation, hence inhibition the IL-1 could have beneficial effects on coagulopathy (43,44).

2. Adult patients with RT-PCR test confirmed COVID-19 and bilateral lung infiltration in chest x-ray were evaluated prospectively in this study (45). Enrollment criteria included: 1) respiratory rate >30 breaths/min and peripheral capillary oxygen saturation (SpO2) of <90% on room air; 2) SpO2 ≤ 93% on oxygen ≥ 6 L/min; or 3) acute respiratory distress syndrome (ARDS). Patients who refused to participate, or were already on invasive mechanical ventilation, or reported a history of diagnosed allergy to anakinra, were pregnant or breastfeeding, or diagnosed with active or untreated tuberculosis, or were at risk of gastrointestinal perforation (abdominal surgery, active inflammatory bowel disease, or active endoscopy proven peptic ulcer disease), or were diagnosed with active cancer, active bacterial or fungal infection or had chronic liver disease, an absolute neutrophil count of $<1.5\times 10^9$/L, or platelet count of $< 50\times10^9$/L, were excluded from the study.

Patients in interventional group received anakinra (N=45) and were compared to a control group of patients who fulfilled all inclusion and exclusion criteria and received standard treatment only (N=24). In anakinra treated patients, the first day of receiving anakinra was considered as day 0 and in historical control group, the day which patients met inclusion criteria was considered as day 0.

Anakinra dosing was adjusted for patients who had reduced renal function (GFR<30 mL/min) or were under dialysis; maximum treatment duration was 10 days. The standard treatment protocol for SARS-COV-2 infection was parenteral β-lactam antibiotics IV ceftriaxone or IV piperacillin-tazobactam) plus IV azithromycin and prophylaxis against thromboembolic events with enoxaparin. Also, corticosteroids were administered in both groups, some patients received a maximum doses of intravenous dexamethasone (6 mg daily) before assigning to the investigation and some patients had received full course of methylprednisolone in historical

group (40 mg BD for 5 days) the authors did not clarified which patients received corticosteroids.

Analysis showed that need for invasive mechanical ventilation was significantly higher in control group (75% vs 31%; p< 0.001). This statistical difference in one of the main outcomes, remained statistically significant after adjustment for multiple variables (adjusted odds ratio (aOR) 0.27; 95% confidence interval (CI) 0.07–0.97; p = 0.046). Also, similar to this finding was observed at day 4 (20% in anakinra group need to invasive mechanical ventilation vs 58% in control group; p=0.033) and at day 14 (23% vs 50%; p=0.046). But evaluating the effect of anakinra in patients who required non-invasive mechanical ventilation and their respiratory failure progressed, did not show any positive effects in terms of requiring invasive mechanical ventilation. The authors of this study concluded that low dose subcutaneous anakinra might not be effective in patients with advanced respiratory failure and the therapeutic window should be considered for its initiation. Evaluation of patients in terms of requiring supplemental oxygen at day 14 showed statistically significant difference between two groups. The number of patients who breathed without supplemental oxygen was higher in anakinra group (63% vs 27%; p=0.008). In contrast to these finding, in-hospital death rates, was not statistically different between two groups (29% of anakinra group vs 46% of control group; p=0.082).

Patients who had high level of inflammatory biomarkers (CRP > 150 mg/L, or IL-6 > 60 pg/mL, or ferritin >1500 mg/L) in two groups, were considered as experiencing hyperinflammation. In comparing two groups, a greater number of patients in anakinra-treated group fulfilled the criteria for hyperinflammation (73% vs 71%). But anakinra showed positive effects in preventing invasive mechanical ventilation and improved respiratory outcomes in both group of patients who were categorized as experiencing hyperinflammation or free of this

complication. The limits of biomarkers that were used for categorization of patient's hyperinflammation status, might have been set too high and some patients in early phases of hyperinflammation may have not been categorized properly and were deemed as patients not in hyperinflammatory state.

The normal level of inflammatory biomarkers at day 14 or discharge were significantly lower in anakinra group (IL-6: 6.6 pg/mL vs 124 pg/mL, $p < 0.001$; CRP: 9 mg/L vs 94 mg/L, $p=0.001$; D-dimer: 0.9 mg/L vs 3.7 mg/L FEU, $p = 0.001$; and LDH: 278 U/L vs 485 U/L, $p = 0.011$).

No injection site reactions occurred in either group of patients, Brevibacterium sp was found in blood culture of one of the patients in anakinra group but the rates blood stream infection due to Staphylococcus epidermidis was similar in both groups. The occurrence of the other adverse outcomes was not significantly different between two groups.

Differences between two groups in receiving other therapeutic options could have caused conclusion bias. The proportion of patients who received longer courses of corticosteroids in historical control group was significantly higher compared to anakinra group (54% vs 2%; $p < 0.001$), this could have reduced the mortality rates in control group considering the proven beneficial effects of corticosteroids. the mortality rates in that group (46). Also, hydroxychloroquine in combination with azithromycin were administered in 21% of historical groups but no patient in anakinra group received this combination. Based on the previous studies combination of hydroxychloroquine and azithromycin could increase mortality rates in COVID-19 patients (47). These two differences could justify the reason why anakinra did not show beneficial effect on mortality in comparison to the historical control group.

Limitations of this study included small sample size, not using a validated randomization method, and presence of non-contemporaneous bias, considering that two groups were not evaluated at the same time and they were compared over a 10-weeks period which might have created reporting errors. It should also be noted that some of the important and effective variables were significantly different between two group and this could have caused bias.

In brief, this study has showed that receiving subcutaneous low dose of anakinra is an effective therapeutic option, in patient with severe COVID-19 who require oxygen and does not have advanced respiratory failure, and by reducing inflammatory biomarkers and controlling hyperinflammation could prevent progression of respiratory failure to need for invasive mechanical ventilation. Anyway, this agent may not have a beneficial effect on mortality rates of these patients if it is initiated late in the course of disease when profound hyperinflammation is present.

3. Patients with RT-PCR test confirmed COVID-19 and typical findings of the infection on their chest CT scan who were admitted to ICU for mechanical ventilation were prospectively evaluated in this study (48). Patients with immunosuppression or other comorbidities that could affect prognosis of COVID-19 infection (not specified by the authors), were excluded from study.

Anakinra was initiated in patients who had evidence of mild hyperinflammation (defined as sustain high degree of body temperature, ferritin $\geq$ 900 ng/ml or CRP $\geq$ 100 mg/L or both and/or progressive organ dysfunction without any other reasons).

Patients who received anakinra (N=21) were compared with patients who fulfilled inclusion criteria but received SOC (N=39).

The day which anakinra was started in intervention group, was considered as day0 and in SOC group the median day of anakinra initiation in intervention group was considered as day 0 (12 days after admission to the ICU). These days were considered as alignment day.

Data analysis showed significant differences between two group at different time points. Patients in anakinra group had higher levels of ASAT (aspartate aminotransferase) (96 vs 64 U/L; p=0.009), ferritin level (2365 vs 1410 µg/L; p=0.001), body temperature (39.1 vs 37.8 °C; p=0.0002) and procalcitonin (0.66 vs 0.48; p<0.0001) on alignment day. CRP levels were not significantly different between two groups on alignment day (p=0.3). Higher levels of these markers in anakinra group could indicate better efficacy of anakinra. The decrease observed in CRP levels in patients who received anakinra was not significantly different compared to patients in control group.

Concentrations of circulating cytokine, decreased during the time between ICU admission and alignment day. After initiating anakinra the concentration of circulating IL-1RA increased significantly (p<0.0001), which was expected because of anakinra mechanism of action. No differences between-group in circulating IL-6 or other cytokine levels was detected over evaluation time. Increased level of circulating IL-1RA after starting anakinra is considered a false positive finding because of pseudo increase in anakinra bound IL-1RA concentration. Therefore, the concentration of this cytokine and the other cytokines after starting treatment are not good of immunomodulating effect of anakinra.

In this study 75 inflammatory markers were monitored in two groups of patients; in patients who received anakinra 17 pro-inflammatory proteins were decreased but none of these markers changed in control group. Because of the large number of measured proteins and correction for multiple testing, statistical significance was not reached.

Body temperatures in anakinra group were significantly higher than control group during 10 days before receiving anakinra (p=0.02) but after treatment with anakinra it was significantly lower in anakinra group (p=0.03). Also, ferritin and procalcitonin plasma level analysis showed similar results (p=0.003, p=0.001)

In patients who received anakinra, reduction in levels of creatinine and bilirubin were significantly higher compared to patients in control group. WBC count increased in control group while it decreased in intervention group after receiving anakinra (p=0.02).

Some parameters did not show any significant differences between two groups based on the analysis. These markers included thrombocyte counts, PaO2/FiO2 ratio or total SOFA score. Also, there were no between group differences in number of patients who received remdesivir and chloroquine as their treatment regimen.

At baseline, norepinephrine infusion rate was significantly higher in anakinra group compared to the control group (p=0.005) but after treatment with anakinra no significant difference was observed.

Before alignment day, the number of patients who received corticosteroids was numerically lower in anakinra group (5% vs 26%; p=0.08). Similar difference remained after starting anakinra (14% vs 28%; p=0.14). Receiving corticosteroid could affect the result of study due to anti-inflammatory effects of these medications and this might decrease mortality rates (49)(50)but sensitivity analysis, which eliminated patients who have received corticosteroid, showed similar results to the primary analysis.

Based on the reporting data, outcomes including secondary infection, time on mechanical ventilation, and ICU length of stay and 28-day mortality were not improved in anakinra group, although inflammatory markers were significantly decreased. Despite these finding kidney and

liver improvement in anakinra group was higher than control group. Lack of improvement or reduction in mortality rate in anakinra group is in contrast to the reports of previous studies (51) and it may be due to inclusion criteria applied. Only COVID-19 patients who were critically ill and required mechanical ventilation were enrolled in this investigation to receive anakinra, while previous studies, which reported beneficial effects with anakinra in COVID-19 patients, included patients with less severe disease who did not need mechanical ventilation. Therefore, anakinra maybe more beneficial in early stages of the diseases when higher levels of cytokines are yet to be observed and this could prevent progression to severe illnesses and admission to the ICU.

Previous studies have shown that hyperinflammation/MAS increase mortality rates in sepsis patients. Administration of anakinra to patients with sepsis and hyperinflammation/MAS, could decrease mortality rates to levels similar to patients with sepsis without hyperinflammation/MAS (52). Based on these experiences, and considering the fact that concentrations of some of the inflammatory markers were significantly higher at base line in patients who received anakinra, the similar mortality rates observed in two groups might confer a beneficial effect of anakinra. Obvious signs of hyperinflammation were present in patients who received anakinra, whereas patients in control group did not show similar characteristics. Therefore, determining efficacy and optimal time of anakinra initiation in critically ill patients with hyperinflammation was not possible.

However, this study was not a randomized control trial, so patients in two group did not have similar prognosis at the time of alignment. Another limitation of this study was that the investigators performed propensity score matching based on patient characteristics, and yielded similar results. An additional sensitivity analysis using a subgroup of control patients

who partially met the criteria to receive anakinra was performed to address this possible bias by indication. Although this matching was not perfect, (as the presence of fever was shorter, ferritin was somewhat less elevated and patients had no signs of progressing organ failure), this group was better matched to the anakinra group than the initial control group used for the main analyses. This additional sensitivity analysis also showed a more pronounced decrease in clinical inflammatory markers in the anakinra group compared to the control group.

It is worth noticing that this study used a very high dose of intravenous anakinra and concluded it was not effective but due to above mentioned limitations and the between group difference in prognosis, the result of study might not be greaseable.

4. COVID-19 patients with moderate to severe ARDS, hyperinflammation (defined as CRP ≥ 100mg/L, ferritin ≥ 900ng/ml or both), who did not require invasive mechanical ventilation or admission to ICU, with no evidence of bacterial infection, and age ≥ 18 years were included in this study (51). SARS-COV-2 infection was confirmed by rRT-PCR and chest radiography or CT scan in all patients.

Patients who were receiving anti-inflammatory agent or glucocorticoids and were enrolled in other clinical trials were excluded.

Included patients received either SOC (N=16), high dose anakinra (N=29) or low dose anakinra (N=7). Patients who were enrolled in high dose anakinra group were numerically younger than SOC treatment group. Patients were monitored for 21 days, or until discharge from hospital, admission to the ICU, or death.

All patients received hydroxychloroquine and lopinavir with ritonavir. In high dose anakinra group, patients received intravenous anakinra until clinical improvement and better respiratory function with PaO2:FiO2>200 mmHg for at least 2 days or bacteriemia, or death occurred.

Following discontinuation of high dose anakinra patients received low dose anakinra 100 mg subcutaneously twice daily, for 3 days in order to avoid inflammatory relapse. The median duration of treatment with high dose anakinra was 9 days (IQR 7–11).

In low dose anakinra group, 7 patients received anakinra 100 mg two times a day subcutaneously. Patients in this group, had ARDS, hyperinflammation, and were receiving oxygen by CPAP and were not admitted to the ICU. Low dose anakinra was discontinued after 7 days because of lack of clinical and respiratory improvement in these patients.

The mortality rate within 21 days was significantly lower in patients who received high dose anakinra compared to SOC group (10% vs 44%) with higher cumulative survival than SOC (90% vs 56%, p=0.009). Pulmonary thromboembolism (N=1), respiratory insufficiency (N=1) and multi organ failure (N=1) were the reasons of death in patients who received high dose anakinra. In SOC group, 3 patients with respiratory failure, 3 patients with multiorgan failure and 1 patient with thromboembolism died. At the baseline, more patients with severe ARDS were enrolled in intervention group (86% vs 56%) while more patients with moderate ARDS were enrolled in SOC group (44% vs 14%). Patients in intervention group were on non-invasive-mechanical-ventilation for longer periods of time and more percentage of them required invasive mechanical ventilation (17% vs 6%) within 21 days of monitoring. But analysis showed that, there were not any significant differences between two groups in cumulative mechanical ventilation free survival (anakinra 72% vs SOC 50%, p=0.15) and the proportion of patients who were discharged from hospital with resumption of normal activities were similar in two groups.

The median baseline ferritin levels in standard treatment were higher than intervention group. Statistically significant difference in level change in CRP and PaO2:FiO2 were not reported

between two groups. But high dose anakinra was associated with progressive decrease in level of CRP, while the levels of this marker sustained or increased in patients who received SOC. Moreover, based on PaO2:FiO2 ratio the respiratory improvement was progressive in intervention group while there was little change in SOC group observed.

Anakinra was interrupted suddenly due to adverse event, without any previous dose tapering in 7 patients but inflammatory condition was not worsened.

The study limitations were small sample size, retrospective design and comparison with a historical control group, so the results might be not conclusive and generalizable. Anyway, this study showed that the high dose of intravenous anakinra could be safe and effective in COVID-19 patients with ARDS and hyperinflammation who were not admitted to the ICU. Due to the study exclusion criteria, results of this study are limited to especial population of COVID-19 patients, because based on evidences using dexamethasone in COVID-19 patients has beneficial effects and recently dexamethasone is included in COVID-19 treatment protocols. Also, some trials which were mentioned in this review, reported that patients with severe COVID-19 who received corticosteroids in combination to anakinra had better outcomes.

5. In this retrospective cohort study (53) COVID-19 patients with hyper-inflammation (defined as ferritin>1000 ng/ml and/or d-dimer > 1.5 μg/ml and IL-6 < 40 pg/ml), ARDS (defined as bilateral infiltration in the chest X-ray or CT with PaO2/FiO2 ratio<300 [based on 2012 Berlin criteria]) and confirmed SARS-COV-2 infection by RT-PCR were included. Patients with IL-6 > 40 pg/mL received tocilizumab, while those with IL-6 > 40 pg/mL and at least a 5-fold increase in liver transaminases levels or contraindication to tocilizumab received anakinra. All patients started treatment after a minimum of seven days from symptom onset.

Overall, 9 patients received anakinra and their outcomes were compared to those of historical control group that received tocilizumab (N=18). Eight out of nine patients in anakinra group, received anakinra with the study dose. In one of the patients who received anakinra with the study dose, treatment was prematurely discontinued after 1 day due to presumed lack of efficacy. Five patients in anakinra group had baseline CRP levels of more than 50 which is associated with poor prognosis. Other drugs that were used in patients who received anakinra were, methylprednisolone in 5 patients before anakinra initiation, and concomitant methylprednisolone in 8 patients. Also, two patients received tocilizumab prior to anakinra. Receiving corticosteroids and tocilizumab in these patients might have affected the study results. All patients who received anakinra, had sign of ARDS and median PaO2/FiO2 ratio of 193 which shows severe impairment of oxygenation at the baseline. Time until administration of immunomodulator therapy (14 days vs 10 days, p=0.033) and hospital stay prior to administration of immunomodulator therapy (median 4 days vs 2 days, p=0.014) were significantly higher in anakinra group. These differences might show that anakinra was used after failure of tocilizumab treatment. On average anakinra was started at day 14 after symptom onset and at day 4 after admission. Favorable outcomes including improvement of PaO2/ FiO2 ratio, decrease in oxygen requirement and inflammatory biomarkers was observed in 5 patients of anakinra group (55.6% of cohort) and 16 patients of tocilizumab group (88.9%). The median days which patients were discharged from the hospital after starting the drugs was same in both groups (14 days).

At day 7, drop in level of IL-6 and ferritin were significantly higher in anakinra recipients and CRP level of patients in two groups were significantly decreased. Also, the level of

improvement in PaO2/FiO2 ratio was significantly higher in tocilizumab recipients than anakinra recipient at this time.

Due to small sample size, lack of placebo control group and presence of confounders, a definite conclusion might not be reasonable.

6. In this randomized controlled clinical trial (54), RT-PCR confirmed COVID-19 patients with typical evidence of the disease in chest CT scan and had mild to moderate or severe critical pneumonia which was defined as receiving oxygen at a flow of >3 L/min via mask or nasal cannula and a score of ≥5 points on the WHO Clinical Progression Scale [WHO-CPS] 10-point ordinal scale. Also cohort patients were eligible for the CORIMUNO-ANA-1 trial if they had a CRP level of >25 mg/L, not requiring admission to the intensive care unit at the time of admission, and mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving at least 3 L/min of oxygen but without ventilation assistance (e.g., high-flow oxygen, non-invasive ventilation, or mechanical ventilation). Patients who were pregnant, or had ANC $\leq 1.0 \times 10^9$ /L, platelet $< 50 \times 10^3$/L, ALT and AST 5 times more than upper limit of normal, estimated GFR< 30 mL/min, or hypersensitivity to anakinra or excipients were excluded.

Overall, 116 patients were randomly enrolled to the standard treatment (ST) group (N=57) or anakinra group (N=59). Two main primary outcomes were: 1) percentage of patients who died or received non-invasive or mechanical ventilation on day 4, defined as more than 5 points of WHO-CPS, or 2) patients who remained alive without non-invasive or mechanical ventilation on day 14. These outcomes were determined by WHO for measuring minimal clinical outcome of patients with COVID-19 infection (55).

In intervention group, anakinra was ordered intravenously for 5 days and patients were evaluated on the morning of day 4, to evaluate their level of oxygen requirement and add a

three-day course of treatment with initial dose in case reduction in oxygen requirement was not more than 50% following this prosses the dose of anakinra was tapered. Treatment with anakinra was initiated 1 day after randomization. Patients in intervention group received anakinra for 2 to 15 injections with a median of 11 injections (IQR 9-15). The median dose of anakinra was 180mg (IQR167-186) and the median cumulative dose of anakinra was 1900mg (1500-2700).

SOC included antibiotics, antivirals (Lopinavir-ritonavir or lopinavir), anticoagulants, corticosteroids (Dexamethasone, Prednisone/prednisolone, Methylprednisolone, Hydrocortisone), hydroxychloroquine and vasopressor support which were ordered per attending clinician's opinion. Some of the patients in both groups received these medications before or after randomization but the percentage of patients was not different between two groups. One patient (2%) received tocilizumab in intervention group.

There was no significant difference in primary outcomes between two groups (47%; 95% CI 33–59 vs 51%; 95% CI 36–62) on day 14. Sensitivity analysis also showed that on day 14, there was not any significant difference between two groups in need for mechanical ventilation or death (34% vs 35%; anakinra vs ST).

At baseline, levels of D-dimer were significantly lower and levels of ferritin were significantly higher in patients who received anakinra. Patients in anakinra group had lower oxygen requirements (1 liter less flow rate) compared to control group, while same SpO2 were reported, this might indicate better baseline condition in patients enrolled to anakinra group Although mortality rates were apparently lower on day 14 in anakinra group (15% vs 24%), post hoc analysis showed that there was no significant between groups difference in mortality rates of patients with CRP<150 mg/L or patients who had received corticosteroids.

Significantly more adverse events were observed in group of patients who have received anakinra (113 vs 60; p=0.0004 for the average number of events per patient). Numerically more serious adverse events occurred in anakinra group compared to ST groups (46% vs 21%; p=0.45). Similar findings were recorded about some important infectious complications and showed that although numerically more bacterial and fungal sepsis occurred in anakinra group (11 vs 4) the difference was not statistically significant (p for all bacterial sepsis=0.099).

In brief, this study showed that anakinra with a dose of 400mg intravenously for 3 days, with possibility of course extension in case of no obvious positive effects, in patients with mild to moderate COVID-19 pneumonia did not show any beneficial effects on primary outcomes. Therefore, lower mortality rates which has been reported in anakinra recipients in previous studies might be because of high mortality rates in control groups. Anyway, these conclusions may not truly represent the anti-inflammatory or positive effects of anakinra, considering the low dose of drug used. The final results of this study indicate that hyperinflammation in patients with mild to moderate COVID-19 may be the consequence of interaction of a combination of inflammatory markers and not just the IL-1 (56).

Considering the multicenter nature of the study, patients might have received different standard treatments in different centers and this may be one of the limitations of the study. Other limitation that might affect the results of the study is the non-placebo-controlled design. Strict inclusion criteria which were used for patient enrolment, limits the generalizability of results.

7. In this retrospective observational study (59), inclusion criteria were defined as positive RT-PCR, bilateral pneumonia on chest x-ray or CT-scan, deteriorating respiratory function and ARDS, all patients had a PaO2:FiO2 ratio of less than 250 mmHg on inspired air, and required ventilation with CPAP or orotracheal intubation, high levels of inflammatory biomarkers

including CRP ≥ 10 mg/dl, or ferritin ≥ 900 ng/ml or both, considered an evidence of ARDS, caused by overstimulation of immune system (57). patients with following characteristics were excluded: not on positive pressure ventilatory support, who received remdesivir, corticosteroids, or any other immunomodulating agents except anakinra. The group of patients who had received anakinra were compared with a cohort of control patients with the same diagnosis at same time who did not receive any other immunomodulating agent.

All patients received lopinavir/ritonavir plus hydroxychloroquine as antiviral agents, azithromycin orally plus ceftriaxone and 4000 IU of enoxaparin daily which was adjusted based on thrombotic risk and D-dimer levels according to hospital protocol (58,59). Beside these routine treatments, anakinra was administered for the patients of intervention group. The duration of treatment was 7 days patients in ward, received 100 mg of SC anakinra four times a day and patients in intensive care units, received 200 mg of IV anakinra three times a day due to the anasarca and SC edema which was observed more frequently in intensive care unit patients. The biomarkers were followed up for two weeks and the primary endpoint was 28 days survival.

Overall, 56 patients received anakinra and 56 patients were in the control group. Among all 112 patients, most of them were male (77.7%) and received CPAP as main oxygenation method (78.6%) at the baseline. The most common comorbidity observed was hypertension (59 patients = 52.7%) and symptom duration before hospital admission was 7 days (IQR: 5-10 days).

Comparing the baseline information of two groups, demographic data including sex, age, CPAP as oxygenation, or Charlson comorbidity index were not significantly different. Patients

in anakinra group had significantly higher median CRP (p=0.021) and D-dimer (p=0.025) at the baseline.

Significantly higher proportion of patients survived at 28 days in anakinra group in comparison to the SOC treatment (75.0 versus 48.2%, p = 0.007). Factors associated with lower survival rates were preexisting hypertension (OR, 0.37; 95% CI, 0.17–0.82), ischemic heart disease (OR, 0.35; 95% CI, 0.13–0.95), and older age (OR per 1 y older, 0.87; 95% CI, 0.82–0.93). Multivariate analysis showed that anakinra did not improve 28day survival but a lower cumulative risk of death was observed in this group (p=0.027).

Some factors were found as predictors of death by univariate analysis including receiving anakinra (hazard ratio [HR], 0.50; 95% CI, 0.28–0.89) age (HR per 1 y older, 1.09; 95% CI, 1.05–1.14), baseline ratio of partial pressure of oxygen in arterial blood to fractional concentration of oxygen (HR per 10 mm Hg higher, 0.95; 95% CI, 0.92–0.98), preexisting hypertension (HR, 2.79; 95% CI, 1.49–5.19), and ischemic heart disease (HR, 1.95; 95% CI, 1.01– 3.75) but multivariate analysis, which was adjusted for all significant factors in univariate analysis, showed that anakinra was not a significant predictor of better survival (OR, 0.94; 95% CI, 0.44–2.15). The 90-days survival was significantly higher in anakinra treated patients (p=0.036). Analysis among patients who were on CPAP at the baseline showed that receiving anakinra was associated with a higher rate of cumulative invasive ventilation-free survival (p = 0.048). In comparison of two groups, anakinra significantly reduced CRP and ferritin levels during 7days of treatment (p<0.001 and p=0.018), also, the lymphocyte count was significantly increased in anakinra group in this period (p=0.049) and same results were maintained by day 14. Previous studies showed that the level of lung involvement and clinical

deterioration were associated with higher level of inflammatory markers so this effect of anakinra could conclude better outcome (60).

The role of anakinra in patients with COVID-19–related severe or critical ARDS may be the result of IL-1/IL-6 axis blockade, which may be associated with inflammation control and possible relief of the ARDS trigger and cytokine storm associated with COVID-19.

The authors of the study concluded that effects of anakinra might be better seen in patients receiving CPAP at the baseline compared to those on higher levels of ventilator support. It should be noted that low number of intubated patients were enrolled in the study and this might have prevented a clear conclusion about the drug's beneficial effect.

8. It is an ongoing open-label non-randomized trial for evaluating the role of level of soluble urokinase plasminogen activator receptor (suPAR) as predicting factor for early initiation of anakinra to prevent Severe Respiratory Failure (SRF) in patients with lower tract respiratory infection was conducted (61). Previous investigations demonstrated that the high levels of suPAR (6µg/l) is one of the indicators for developing SRF in the following 14 days (62,63). Overall, 130 patients were enrolled to the intervention group. While 179 cases received the SOC treatment (SOC) in parallel to intervention group, 130 fully matched patients were selected by propensity score-matching. The concentration of suPAR was measured by collecting blood of all patients at the baseline and on day 7.

Adult hospitalized patients who had positive result of RT-PCR test for COVID-19, evidence of lower respiratory tract infection on chest radiography and plasma suPAR level $\geq$ 6µg/l were enrolled in the study. Exclusion criteria were any stage 4 malignancy, PaO2:FiO2 $\leq$ 150 mmHg, need of MV or NIMV under positive pressure, primary immunodeficiency or receipt of corticosteroid at baseline with dose of $\geq$ 0.4 mg/kg prednisolone or equivalent in the last 15

days, receiving any anti-cytokine biological treatment in the last month, neutropenia (<1500/mm^3), pregnancy or lactation.

The following differences between two groups were shown in multivariate Cox regression analysis: Incidence of developing SRF during 14 days was significantly higher in SOC treatment (59.2% vs 22.3%; p=0.0001), anakinra was the only independent variable which protect patients from SRF (hazard ratio 0.28; 95% CI, 0.18–0.44; p<0.0001). Although more patients who developed SRF received dexamethasone, it was not considered as a cause of SRF, because separate multivariate analysis among patients who received dexamethasone showed that the anakinra was only independent protective factor against SRF. Anakinra was only independent protective factor against 30day mortality (hazard ratio 0.49; 95% CI 0.25–0.97; p=0.041). Also, 90day mortality was significantly lower in anakinra group (16.9% vs 30.8%; OR:0.46; 95% CI:0.25–0.83; p=0.013). Patients in anakinra group survived more days without ventilator until day28and median total cost of hospitalization decreased with receiving anakinra.

IL-10/IL-6 ratio is considered an index of anti-inflammatory/proinflammatory balance in severe COVID-19 compared to bacterial sepsis (64). This index was inversely associated with the absolute elevation in SOFA score on day 14 in patients who received anakinra and was compatible with the anti-inflammatory effect of anakinra in this group of patients. Concentrations of suPAR was increased significantly in anakinra group on day 7 compared to baseline. Despite this elevation, anakinra was able to protect patients from developing SRF.

Before macrophage activation and deterioration of condition in patients with CVID-19 infection (65) some biomarkers such as sIL2-R and sCD163 increase (66). Anakinra could decrease this elevation and prevent macrophage activation.

Based on the results of this investigation, early anakinra initiation based on the concentration of suPAR is considered a good strategy for protecting patients against SRF. Restoration of the pro-inflammatory/anti-inflammatory balance by increasing anti-inflammatory effect might be the mechanistic action of anakinra.

9. This investigation was conducted to identify the therapeutic window of IL-6 and IL-1 blocking agent in order to maximize their therapeutic actions. the effects of anakinra, tocilizumab and sarilumab, which were initiated according to the baseline respiratory impairment, were compared to the SOC (67).

SARS-COV-2 infection confirmed by RT-PCR test and evidence of bilateral pneumonia in all patients. Inclusion criteria consisted of severe COVID-19, defined as PaO2/FiO2 ≤ 300 mmHg while receiving high flow oxygen, and hyperinflammation defined as high level of LDH and at least one of the following levels: CRP ≥ 100 mg/L; IL-6 ≥ 40 pg/mL; or ferritin ≥ 900 ng/mL. The patients were excluded if their duration of hospitalization was more than 4 days, have received concomitant or previous immunosuppressive drugs, uncontrolled systematic infection, were on mechanical ventilation, neutrophil count was less than 1500/mm^3, diverticulitis/diverticulosis, the levels of AST or ALT was 5-fold more than upper limit normal, or were pregnant. Patients who were admitted to the ICU or died during the first 24 hours after enrollment were also excluded.

All patients received SOC that contained oral lopinavir/ritonavir, hydroxychloroquine, and empiric antibiotic for community acquired/hospital acquired pneumonia (intravenous ceftriaxone or azithromycin). Due to ARDS which was defined as PaO2/FiO2 ratio <300 with a PEEP ≥5 cm H_2O, all included patients received high flow oxygen or were placed on NIV.

Anakinra continued until achieving clinical benefit (sustained improvement in respiratory parameters).

Overall, 210 patients fulfilled the inclusion criteria, of those 107 (50.9%) patients received biologic agents beside the SOC (48.6% anakinra, 28% tocilizumab; and 23.4% sarilumab)

A total 57 patients died following enrolment after a median follow-up of 111 days (3-186), the incidence of mortality was higher in SOC group (34.9% vs 19.6%) which shows that receiving biologic drugs was associated with lower risk of mortality (HR 0.48; 95% CI0.29-0.81; p = 0.006). In order to evaluate the efficacy of biologic drugs, comparison between patients who received different medication and matched control group showed that anakinra provided a statistically significant lower mortality risk (HR 0.47; 95% CI 0.26-0.87; p = 0.01) but sarilumab and tocilizumab did provide this effect.

Multivariate analysis in biologic group, showed that older age, high level of LAD (lactate dehydrogenase) and low PaO2:FiO2 ratio at the time of drug infusion were independent predictor of COVID-19 related mortality.

Moderate and severe ARDS defined as PaO2/FiO2 ratio ≥ 100 mmHg and PaO2/FiO2 ratio < 100 mmHg. A hundred and one patients had moderate ARDS, of those 42 patients received IL-inhibitors and 59 patients received only SOC. Baseline Clinical condition, inflammatory markers and epidemiological factors were similar in two groups. The incidence of death was higher in SOC group after a mean follow-up of 113 days (HR 0.23; 95% CI 0.1-0.55; p = 0.001). Multivariate analysis showed that elevation in ferritin (p=0.01) level and treatment with SOC (p=0.01) were independently associated with death. Patients who had moderate ARDS and received biologics had significantly higher rates of survival compared to matched comparator ($p < 0.05$).

Overall 109 patients had severe ARDS of those, 65 received an IL-inhibitors and 44 patients received only SOC. After a mean follow-up of 110 days the incidence of death was not significantly different between two groups (p=0.21) but multivariate analysis showed that patients who received anakinra (not sarilumab or tocilizumab) had lower mortality rates compared to SOC group (HR 0.46; 95% CI 0.22-0.94; p = 0.04).

The authors mentioned that the study was started prior to availability of reports showing beneficial effects of corticosteroids which might have limited the potential therapeutic confounders. Non randomized, retrospective and observational design of the study also limits the applicability of findings.

Anyway, this study reported that if IL-1 and IL-6 inhibitors, initiated early (before severe ARDS), could decrease mortality. This survival advantage remains significantly higher in patients who receiving anakinra even initiated in patients with severe ARDS condition. When decision is made to start IL blockers a therapeutic window should be considered.

response to IL-1 or IL-6 blocking strategies in patients with COVID-19 depends on the degree of respiratory impairment at the time of treatment administration and underscore the existence of a window of opportunity in which cytokine-blocking agents - as well as of more common anti-inflammatory therapies such as glucocorticoids and colchicine - might effectively counteract rampant inflammation in COVID-19 (49,68)

Anakinra used in combination with or sequential to other therapies

1. A 57-year-old man with a 5 days duration of sore throat, cough and fever was presented to the hospital (69). Laboratory results on day 0 showed increased level of CRP and troponin-1 but no abnormalities in cardiac examinations. Multiple patchy ground-glass opacities and sign of emphysema were revealed by High Resolution Computed Tomography (HRCT) and result of

rRT-PCR assay was reported positive. Lopinavir/ritonavir, hydroxychloroquine, azithromycin, linezolid, Piperacillin/tazobactam, ceftriaxone and enoxaparin were started for the patient. Oxygen saturations dropped in the following days and on day 4 of admission the patient showed signs of severe ARDS (PaO2:FiO2=63) while on venturi mask. After 7 days of hospitalization, patient's clinical condition worsened and his body temperature and inflammatory biomarkers (CRP, D-dimer and ferritin) increased. Severe ARDS progressed as observed by a decrease in the ratio of PaO2/FiO2 to 50. Anakinra and remdesivir started and dose of enoxaparin increased on day 7 of hospitalization. Subsequently patient became afebrile and his inflammatory markers decreased. On day 16 significant improvement in respiratory function was observed and in subsequent HRCT no new findings were detected his new HRCT has shown in consolidation lesion which were previously considered. The patient's RT-PCR results were still positive on day 32, but at that time supplemental oxygen was discontinued and the patient was transferred to subacute care setting. The patient was monitored for 28 days and his of baseline laboratory results during these days were CRP:20 mg/L, D-dimer: 1188ng/ml, and lactate dehydrogenase (LDH):278 U/L and the results on day 28 were CRP: 3.1 mg/L, LDH:278 U/L, d-dimer:1910 ng/mL. The levels of IL-1 and IL-6 were not monitored during hospitalization. Considering that anakinra and remdesivir were started concomitantly for the reported patient, it is difficult to clearly relate the observed beneficial effects to any one of these medications.

2. In this retrospective cohort study, ninety-three patients with COVID-19 who had evidences of cytokine storm (CS) were enrolled (70). CS was diagnosed by a combination of laboratory results (ferritin >2000 ng/mL and one of the other abnormal markers or ≥ 4 abnormal inflammatory biomarkers including CRP >70 mg/L, ferritin>700 ng/ml, D-dimer>1000

ng/mL, triglycerides >265 mg/dL, AST >59 IU/L, LDH > 300 IU/L, lymphocyte count <800 cells/µL and neutrophil count >8000 cells/µL), clinical feature and respiratory function. Due to lack of laboratory results of 17 patients at time of treatment initiation, alternative criteria were defined as if three abnormalities were reported when 4 or fewer previously mentioned laboratory markers were measured or if reports of all 5 laboratory markers in a same day were not available, the results of 2 days before or 2 days after that day were used for diagnosis.

The possible day of COVID-19 CS onset was not exactly identified, but seems like CS started between 8 to 10 days after symptom onset. The treatment strategy for severe form of CS, which occur in context of MAS and HLH, is early treatment with anakinra alone or in combination with corticosteroids and prompt response to treatment, including improvement in fever, hypotension and levels of inflammatory biomarkers, should be observed. If rapid response is not seen, the dose of anakinra should be increased and in some circumstances continuous IV administration of drug might be considered (71,72).

Patients were divided to two groups, 52 patient received tocilizumab, which was initiated at a median of 14 days after symptoms onset, and 41 patients received anakinra which was initiated at a median of 13 days after symptoms onset. Anakinra was given for a median duration of 9 days (6-11 days), and the median cumulative dose was1500 mg (1200-2400 mg).

In patients who received anakinra, lower percentage of intubation and higher percentage of extubation was reported in comparison to patients who received tocilizumab (56.1% vs 96.2; $p<0.0001$). Adjusted analysis failed to show any significant differences between the mortality rates of two groups (PS-adjusted HR = 0.46, 95%CI = 0.18–1.20, p = 0.11). In anakinra group, patients were divided into two subgroups: 1) patients who died while receiving anakinra; and 2) patients who survived. In subgroup 1, patients at the time of death had higher persistent rates

of inflammatory markers that revealed the worsening COVID-19 CS and in subgroup 2, the inflammatory markers were started to lower.

Patients who received tocilizumab had lower rates of obesity (BMI ≥ 30) than patients who received anakinra (50% vs 70%; p=0.04), while more male patients were included in anakinra group (86.5% vs 68.3, p=0.03). The number of patients who were intubated in tocilizumab group was significantly higher than anakinra group at medication initiation (50% vs 23%, p<0.0001), but among patient who were intubated at the first dose, the days on intubation and FiO2:PaO2 ratios were not significantly different between two groups. More tocilizumab-treated patients had body temperature of ≥38°C (61.5% vs 39%; p=0.03. Also, more patients in tocilizumab group developed hypotension and required vasopressors (67.3% vs 31.7%; p=0.0006). More patients in anakinra group fully met the laboratory criteria for COVID-19 CS compared to tocilizumab-treated patients (p=0.04) and the median duration of cytokine storm in anakinra group was longer than tocilizumab group. Concomitant drugs which were received with anakinra or tocilizumab were significantly different between two groups. All patients in anakinra group have received corticosteroids, of those two patients received more than maximum daily dose of corticosteroids. But among patients who received tocilizumab only 7 patients received corticosteroids.

The authors concluded that the factors associated with poor response to tocilizumab and anakinra were neutrophilia, AKI and hypotension which were late finding of COVID-19 CS and were more common at treatment initiation in tocilizumab group. They also mentioned that laboratory abnormalities are predictors for SC initiation and eventually respiratory failure, so poor response in tocilizumab group may be due to not measuring these factors properly. Timely

recognition and management of CS in the context of COVID-19 prior to need for mechanical ventilation could affect the outcomes of therapy greater than the type of agent chosen.

3. The results of a secondary analysis of a prospective observational cohort study were reported in this investigation (28). Patients were enrolled from different setting in different times. The inclusion criteria were: age>18 years; evidence of pneumonia; respiratory failure and need for supplemental oxygen (ranged from FiO2 of 0.4 with venturi mask to invasive mechanical ventilation) and levels of ferritin ≥ 1000 ng/mL and/or CRP>10 mg/dL. Patients who were lost to follow up or died within 48 hours of inclusion, were excluded from final analysis. Also, patients with symptoms duration of less than 7 days, suspected of having uncontrolled bacterial sepsis or sepsis shock, or received only anakinra or methylprednisolone were excluded. Overall, 120 patients were enrolled to this study. Of these, 65 patients were enrolled to intervention groups and received anakinra and methylprednisolone concomitantly. The outcomes of intervention group were compared to a historical control group of 55 patients who received SOC including hydroxychloroquine and lopinavir/ritonavir. The patients were monitored for 28 days after starting treatment. There were no differences between IV or SC route of administration considering the occurrence of adverse events. All patients received enoxaparin as prophylaxis or treatment of thrombotic events. Significantly more patients received enoxaparin in anakinra group compared to control group (63.1% vs 38. %; p=0.009) while more patients in control group received lopinavir/ritonavir (70.9% vs 30.8%; p<0.0001), considering the beneficial effect of enoxaparin and neutral or detrimental effects of lopinavir/ritonavir this might have influenced the results of the study in favor of anakinra (73–76). Some patients were enrolled to the subgroup of patients who received experimental treatment with remdesivir in combination with other treatments. Median age of all patients

involved in both groups was 62 years, 80% of those were male and their median Charlson comorbidity index (CCI) was 0 with recorded median PaO2:FiO2 ratio of 151, median ferritin levels of 1555 µg/mL; and median CRP of 15.2 mg/dL. overall, 32.5% of all the patients enrolled in the study were on mechanical ventilation. More patients with CCI ≤ 1 were involved in control group (25% vs 45.4%; P=0.017). Patients in anakinra group spent more days in hospital before inclusion in the study (3 vs 1 median days; P < 0.0001). Besides, baseline PaO2:FiO2 ratio was lower (median of 142 vs 173; P=0.049), less patients received lopinavir/ritonavir (30.8% vs 70.9%; P < 0.0001), and higher proportion of patients received anticoagulant therapy (63.1% vs 38.9%; P=0.009) in control group. Anyway, patients in intervention group had lower mortality rates compared to patients in control group (13.9% vs 35.6%; P=0.004). At the time of enrollment, the number of patients who were on mechanical ventilation in intervention and control groups were, 18 and 21 respectively. The mortality rate of mechanically ventilated patients was higher in patients of control group (16.7% vs 42.8%; p=0.076).

In brief, this study showed significantly lower cumulative mortality rate in patients treated with combination of anakinra and methylprednisolone compared to historical control group (HR 0.33; 95% CI, 0.15-0.74; P=0.007). The Multivariate analysis, adjusted by for age, sex, baseline PaO2:FiO2 ratio, CCI, mechanical ventilation at inclusion time and days between admission to the hospital and inclusion in this study, showed that treatment with anakinra in combination to methylprednisolone was independently associated with improved survival (HR .18; 95% CI, 0.07-0.50; P=0.001). However, the investigators did not adjust analysis by patients who received antiviral or anticoagulant therapy which could have been associated with lower mortality rates in intervention group. The rate of detection of bloodstream infections

were not significantly different between two groups (13.8% vs 7.3% in control and intervention groups respectively). Considering the single center nature of the study, the results might not be generalizable to other COVID-19 patients treated in different centers, because of different SOC in those centers. The results of this study do not provide data about using anakinra or methylprednisolone alone and this limits the ability to predict therapeutic benefits of each intervention solely, especially anti-inflammatory actions of both medications, which could have provided synergistic effects should be noticed. Patients in SOC group received antivirals and anticoagulants which were not significantly associated with lower mortality but could have caused bias in final analysis. Patients were not followed more than 28 days, following patients for longer time could have provided better data about treatment efficacy in patients with different severities and length of disease.

4. In this prospective cohort study, 143 patients with severe SARS-COV-2 pneumonia and hyperinflammation were enrolled(77). All patients were followed for 60 days after first dose of corticosteroid therapy. Severe disease was defined as positive PCR test; body temperature higher than 38°C for at least 5 days from onset of symptoms and hyperinflammation defined as at least two of the following markers: CRP > 90mg/L, ferritin >500 μg/L, D-dimer > 0.5 mg/L. Severe pneumonia was defined as oxygen saturation of less than 93% or partial pressure of O_2 of less than 65 mmHg and evidence of unilobar or multilobar involvement in chest x-ray or CT scan imaging (78).

SOC was a combination of hydroxychloroquine, azithromycin, lopinavir/ritonavir, ceftriaxone, and bemiparin for thromboembolism prophylaxis with adjusted dose based on thromboembolic event risk. If patients did not have contraindication for electrocardiographic studies this standard treatment was begun for them.

Immunosuppressive treatment was consisted of 3 steps. If patients fulfilled all the mentioned criteria, they would have received step1 and according to the observed clinical improvement and respiratory function, subsequent steps were initiated if required. If no respiratory improvement was observed, next steps were added to the treatment. In patients who were not improved by methylprednisolone (MTP) and had IL-6 level of <40 pg/mL, anakinra could be administered in combination with tocilizumab (TCZ) or alone as second line immunosuppressive therapy. Three steps of immunosuppressive therapy consisted of: 1) MTP 2 mg/kg/day intravenously for 3 days with possibility to continue therapy for another two days, step 2) single dose of intravenous TCZ which was dose adjusted according to the body weight and step 3) subcutaneous anakinra. Dose of anakinra in first day was 100 mg/12 h for patients weighing 50-60 kg, 100 mg/8 h for patients weighing 60-57 kg, 100 mg/6 h for patients weighing >75 kg. Dose of anakinra from second day was 100 mg/12 h up to day 6 in all patients.

Patients were divided to three groups. Patients in group 1, which consisted 52% of the patients, received only MTP, Patients in group 2 which consisted 41% of the received MTP+TCZ, and Patients in group 3, which consisted 7% of the patients (4 patients after MTP and 6 patients after MTP+TCZ) received anakinra in addition to MTP+TCZ. Four patients received anakinra as second line treatment after MTP, of those, one patient had very low levels of IL-6 and three patients received the drug based on medical team decision.

No difference was seen in rates of comorbidities in patients enrolled in different groups. Moreover, demographic data, CURB-65 or qSOFA score or degree of radiological involvement at time of admission were not different between groups. The baseline laboratory

results including levels of CRP, D-dimer, total lymphocytes, or CD_8 count were not statistically different.

The primary outcomes were defined as death and ICU admission in a duration of 60 days following first corticosteroid pulse dose.

Overall, 14 patients died, 8 patients in group 1 and 6 patients in group 2. Multivariate analysis, adjusted for age and clinical severity indices, showed that anakinra could reduce mortality rate (adjusted hazard ratio 0.518, 95% CI 0.265–0.910; p = 0.0437) and overall analysis showed that group 3 had lowest mortality rate among 3 groups (0% vs 11%, 95%; p= 0.0354). More patients in group 2 and 3 were intubated in comparison to group 1 (11.9% in group 2 and 20% in group 3 vs 2.7% in group1) and mean duration of their hospital stay was 4 weeks. These results show that early treatment with anakinra within 48hours after starting corticosteroid alone or with tocilizumab in patients who did not show positive response to the treatments, may be more effective.

The important limitation of this study was that all of the patients in anakinra group were male, which is a known risk factor for disease severity and death, so the results may be not generalizable to women (42).

5. In this study 51 patients who received subcutaneous anakinra plus IVIG were compared with 31 patients who received intravenous tocilizumab (8 mg/kg as a single infusion with a possible repeat dose in especial conditions) (79). All Patients received corticosteroids because of the beneficial effect of it on reduction of mortality rates in patients with COVID-19 (49). The primary outcomes of this study were death and need for intubation and the secondary outcomes were need for ICU admission, length of hospital stay, change in Respiratory rate-OXygenetion

(ROX) index (80), National Early Warning Score (NEWS) score and laboratory results of day 7 and day 14 after starting treatment.

COVID-19 pneumonia was confirmed by findings in CT scan imaging of the chest as evidenced by the presence of bilateral peripheral ground glass opacities, positive RT-PCR test results, high levels of inflammatory biomarkers and lymphopenia. Inclusion criteria were defined as increase in oxygen requirement for maintaining the level of SPO2 ≥93% and, at least two of the inflammatory biomarkers, CRP, ferritin, D-dimer, LDH and cardiac troponin, increased 3times more than upper limit of normal.

There was no significant difference in baseline levels of inflammatory biomarkers between two groups. Baseline respiratory function and NEWS scores (7.5±3.5 vs 5.6±3.5; p=0.017) were worse in patients who received tocilizumab. Although numerically more patients in tocilizumab group required supplemental oxygen via high-flow nasal canula (33.3% versus 17.6%) and mechanical ventilation (24.2% versus 15.7%), the difference was not statistically significant between two groups (p=0.191). The primary and secondary outcome were not statically different between two groups, but analysis showed that patients who died, were older (57.8+12.7 years versus 72.8+ 8.7 years, p<0.0001), more obese (p=0.008), had cardiac and renal comorbidities and more severe disease at baseline. Although, patients who died, had higher levels of inflammatory biomarkers than patients who survived, the baseline inflammatory markers were not different between two groups except for fibrinogen (p=0.007). The findings of this study suggest that response to therapy at day 7 and day 14 might predict the overall response of patients to the treatment, besides persistence of high levels of inflammatory markers was related to poor patients' outcome.

The two important causes of biases were higher severity of disease in patients in tocilizumab group and intravenous route of administration of biologic agent, which is more effective in rapidly deteriorating patients provides quicker treatment response.

The main limitations of this study were lack of randomization and control group which might have led to selection bias, also patient allocation to treatment groups depended on drug availability and anti-interleukin treatment was added to treatment regimen after failure of corticosteroids.

Although, clinical outcomes including death, intubation, need for ICU admission, and hospital length of stay were not statistically different between two groups, comparison of clinical outcome between living and decreased patients showed that there were statistical differences. More patients among those who died, were intubated ($p<0.0001$) and needed ICU admission ($p=0.002$). Also, the change in ROX index from baseline to day 7 and number of patients with secondary infections were higher in living patients compared to deceased patients ($p=0.001$, $p=0.009$ respectively).

In brief, this study showed that subcutaneous anakinra plus IVIG or intravenous tocilizumab did not provide further beneficial effects in COVID-19 patients with cytokine storm.

6. A cohort of patients with severe COVID-19 who received anakinra after failure with tocilizumab were prospectively evaluated in this study (81).

Patients of intervention group (N=20) were compared a group of historical controls (N=20) who only received tocilizumab. Four of the included patients were also included in a previously published study.

SARS-CoV2 infection was confirmed by RT-PCR test and related abnormalities in chest x-ray imaging. Patients with evidence of hyperinflammation in their laboratory reports (CRP≥ 10

mg/dL, ferritin≥ 500 mg/dL or D-dimer≥ 1500 ng/mL), oxygen saturation of <90% received tocilizumab. Patients with bacterial infection, diverticular disease, neutrophil count of less than 1.5×10^3 cells/μL or ALT/ AST more than 5 times upper of limit were excluded.

Baseline data were not significantly different between two groups except lymphocyte value. Median lymphocyte count in control group was higher than intervention group (0.5 vs 0.25; p=0.035).

Tocilizumab was dosed according to patient's body weight. Patients who weighted ≥75kg, received 600 mg while those < 75 kg received 400 mg. Administering a second dose of tocilizumab depended on the physician's opinion. Patients after receiving tocilizumab were evaluated with six-point ordinal scale daily, this scale was considered by WHO for evaluating clinical condition and respiratory function of patients who were infected with COVID-19 and was used in the previous studies (76) if after receiving tocilizumab the daily clinical scales did not show clinical and respiratory improvement, anakinra was ordered for patients.

Duration of treatment with anakinra was at least 6 days. Six days after receiving anakinra, patients were evaluated to make decision about interrupting or continuing the medication. Patients who had bacterial infection and neutropenia (neutrophil count < 1.5×10^3 cells/μL) were excluded.

Standard treatment included supplemental oxygen and supportive care with or without lopinavir/ritonavir, hydroxychloroquine ± oral azithromycin, subcutaneous interferon-β, intravenous boluses of methylprednisolone and antibiotics. No patient received remdesivir concomitantly with tocilizumab and anakinra.

The duration of follow up was until discharge from hospital or death. Patients were evaluated on days 0, 7, 14 and 21 by six-point ordinal scale and changes were recorded. Meaningful

primary outcomes were discharge from hospital and/or a decrease of ≥1 in score, compared to baseline. Change in scores on days 0, 7, 14 and 21 were considered as secondary outcomes.

In the anakinra group the date of administration of the first dose of anakinra was considered as day 0. In the control group, day 0 corresponds to the day on which anakinra would have been started if the same interval between the administration of tocilizumab and anakinra had been maintained as in the corresponding case (pseudo date of treatment).

The median time between receiving tocilizumab and anakinra was 6 days (IQP= 4-8.75) and the median time from onset of symptoms and inclusion in the study was 16 days in two groups (IQR=12-24).

Number of patients who required high flow oxygen, mechanical ventilation and low flow oxygen were same in anakinra and control groups and on day 0 percentage of patients with severe ARDS was not significantly different between two groups (55% vs 40%).

Clinical improvement after 7 days of follow up (25% vs 45%; p=0.185), discharge from hospital on day 21 (30% vs 35%), and in hospital mortality rate (55% vs 45%; p=0.527) were not significantly different between anakinra and control groups. Clinical improvement rate and scores on day 14 and 21 following inclusion were exactly equal in both groups.

Prior studies showed that suppressing the cytokine release syndrome as soon as possible and before development of severe disease was more effective but in this study the times between symptom onset and initiating anakinra was long and most of the patients in two groups (90%) had severe disease at the time of inclusion to the study based on PaO2:FiO2 rate of <200(31,33,45,51). The authors suggested that lack of efficacy of anakinra might have been because of its mechanism of action which is thought to be due to downstream IL-6 blocked so

addition of anakinra to therapeutic regimen of patients who have received tocilizumab might not provide additional beneficial effects (82)

On the other hand, the dose of anakinra in this study is significantly lower compared to dose used in previous studies and this might be the reason for ineffectiveness. Selecting this low dose was based on experiences with use of anakinra in patients with inflammatory rheumatological diseases and no systemic infections (83).

Although a previous study showed beneficial effects with similar low dose of anakinra in COVID-19 patients (33), another study, which compared the effect of high dose and low dose of anakinra in patients with moderate to severe CVID-19, showed that only high dose anakinra had positive effects in these patients (51).

In both groups, enrolled patients had high median of Charlson index score which indicates high level of comorbidity. High rates of mortality in this study, in comparison to the other studies, may have also been due to shortage of ICU beds and ventilators.

In brief, anakinra did not provide further beneficial effects on in-hospital prognosis of COVID-19 patients previously treated with tocilizumab.

7. Retrospectively the effect of early anti-inflammatory treatment (AIT) with anakinra alone or in combination with a glucocorticoid was evaluated in a single center in this study (84). Early AIT was defined as starting treatment within 4 days after admission if patients fulfilled following including criteria: 1) severe COVID-19 which was classified by findings in chest CT scan and RT-PCR test; 2) existence of 1 of 3 following parameters PaO2:FiO2 ratio of 300 mm Hg or lower and plasma level of CRP or ferritin increasing 3-fold higher than upper limit normal; and 3) lymphocyte count lower than 1000 cells/mm^3 and D-dimer or LDH 3-time higher than upper limit normal. Although data from patients who died within 4 days of

admission were excluded in final analysis and this could have biased the results of the study, as these patients might have presented with serious disease and patients in early AIT received treatment in this phase, only two patients were excluded and this limit the confounding effect. Also, patients who had incomplete clinical information or who were older than 90 years were excluded from the study.

In intervention group, patients who were presented to the emergency room and fulfilled the inclusion criteria, received methylprednisolone 1 to 2 mg/kg intravenously once or twice daily, followed by gradual dose tapering, as first drug because using anakinra was not possible immediately. Outcomes of patients in intervention group (AIT) [N=63] were compared to a retrospective control group of patients who received SOC [N=65] who fulfilled inclusion criteria but they did not receive early AIT. The SOC treatment protocol consisted of hydroxychloroquine and/or azithromycin, lopinavir/ritonavir or darunavir /ritonavir, and enoxaparin 4000 IU per day with adjustment of the dose according to body weight, kidney function and level of D-dimer. Anakinra, tocilizumab with a dose of 8 mg/kg up to a maximum dose of 800 mg and glucocorticoids consisted the late AIT in control group who did not receive early AIT regimen.

The anakinra in early AIT regimen was initiated with a dose of 100 mg every 8 hours for 3 days followed by gradual dose reduction, depending on the patient's response to treatment, with the following schedule, 100 mg every 12 hours for 1-3 days then, 100 mg daily for 1-3 days, with Maximum total duration of treatment of 9 days.

All patients received hydroxychloroquine and/or azithromycin. Early AIT group was divided to 2 following subgroups: 1) 30 patients received anakinra alone, 2) 33 patients received anakinra plus a glucocorticoid (glucocorticoids were initiated 1 to 2 days before starting

anakinra and in some patients they were administered in combination with anakinra). Also, control group divided to the following 2 subgroups 1) 44 patients who received SOC treatment alone 2) 21 patients who received SOC treatment followed by late AIT as salvage treatment.

Acute pulmonary thromboembolism, bacteremia and candidemia were the main complications reported in patients during hospitalization. While all patients received enoxaparin, acute pulmonary thromboembolism occurred in 1 patient in each group, bacteremia occurred in 3 patients in each group but candidemia only occurred in 4patients who received early AIT (3 in anakinra subgroup and 1 in anakinra plus glucocorticoid group).

Most of the baseline data were different between 2 groups (Standardize Mean Difference (SMD)>0.1), some of the important differences are mentioned in the following sentences. Although patients in early AIT group were younger (mean: 60.7 vs 67.3; p=0.02) in comparison to the control group, these patients had higher baseline level of inflammatory markers (ferritin [mean:1174 vs 645 ng/mL; p=0.001], CRP [mean: 9.8 vs 7.5 mg/dL; p=0.007] and LDH [mean: 378 vs 306 U/L; p=0.002]) and worse respiratory function at the baseline (lower PaO2:FiO2 ratio, 223 mmHg in AIT group vs 301 mmHg in control group; p<0.001) but overall CRP levels were lower than 10. More patients with comorbidities, mainly cardiovascular disorders, were involved in control group (29.2% vs 12.7%; p=0.03) and patients in this group were older, therefore these factors might have contributed to higher mortality rates (42,85). The proportion of patients who received antiviral agent (38.1% vs 64.6%; p=0.004) was higher in control group but proportion of patients who received enoxaparin (95.2% vs 76.9%; p=0.004)was higher in early AIT group, therefore considering that currently there is no stablished antiviral drug for treatment of COVID-19 (73) and it has

been shown that prophylaxis against thrombosis could definitely lower mortality, these differences may have lowered the mortality rate in early AIT group (74).

Of all evaluated patients, 29% (37) died and 28 patients were admitted to the ICU. The number of patients who were admitted to the ICU was not statistically different between two groups but the percentage of deaths was different and was lower in anakinra group (14% in anakinra group vs 43% in control group). The rate of death in control group was same in patients who received SOC alone or SOC plus late AIT. The rate of deaths in patients who received anakinra plus glucocorticoid was numerically higher than patients who received anakinra alone (15% vs 13%).

IPW-Cox model analysis which considered ICU as time dependent covariant revealed that early AIT has reduced hazard of mortality by 74% (adjusted HR 0.26 [95% CI 5 0.10-0.66]; P < 0.001). Also, multivariate model showed similar result (adjusted HR 0.28; P=0.04). Multivariate analysis showed that early AIT reduced the mortality by 74% (adjusted HR 0.26 [95% CI 0.10-0.66]; P < .001) and the effects observed in patients who received anakinra alone was similar to patients who received anakinra in combination with glucocorticoids (HR 0.28, p=0.04; HR 0.33, p=0.07) respectively. However, it should be noted that only one patient received anakinra in combination with a glucocorticoid in early AIT group in patients who received late AIT in control group, no beneficial effect was observed (adjusted HR 0.82; P=0.70).

Comparing groups for level of inflammatory markers and respiratory function, showed that improvement of these markers was observed shortly after initiating early AIT but no significant difference was reported between two subgroups of patients in terms of change in PaO2:FiO2 ratio, LDH level and requiring respiratory support. Improvement in CRP levels occurred in

significantly shorter time in patients who received anakinra plus glucocorticoid (mean time: 9.8 days±8.1 vs 16.8 days ±10.8; p=0.011).

Patients in anakinra plus glucocorticoid subgroup were not enrolled according to the randomization protocol or special subgroup inclusion criteria if these patients fulfilled all study inclusion criteria and were admitted to the emergency department, glucocorticoids were immediately ordered in case of anakinra shortage. But longitudinal analysis showed that using glucocorticoids as an adjuvant treatment in combination with anakinra could result in reduction of inflammatory markers faster than anakinra alone, although, the safety of this practice is not clarified.

In the analysis of this study, it was tried to eliminate the effects of interfering factors, but the authors mentioned that part of survival benefit observed with anakinra could have been because of optimized overall management of critically ill patients during the study period.

This study provided useful information about safety and efficacy of the early anti-inflammatory treatment with high dose intravenous anakinra with or without glucocorticoids in severe COVID-19 patients. This investigation showed that using high dose of AIT (anakinra) as soon as possible in hospitalized patients who require oxygen support, could improve inflammatory and respiratory status in most of the cases with severe COVID-19. It was also demonstrated that prescribing glucocorticoids in combination with anakinra might be a reliable approach to achieve positive effects in decreasing inflammatory markers, although this regimen failed to improve survival rates.

Possible effects of anakinra on humoral response to SARS-CoV2

In order to identify the variables that could have affected the humoral response to COVID-19, patients with confirmed or suspected SARS-COV-2 infection were prospectively evaluated. The WHO diagnostic criteria was used for enrolling patients with suspected disease(68).

The results of RT-PCR of 60% of the patients were positive. The mean time between hospital admission to antibody testing was 82 days, the SARS-COV-2 IgG antibody was positive in 82% patients, the rate was higher in patients who had positive RT-PCR test (90% vs 72%) and 94% of patients with positive PCR and no antibody response had no (52%) or minor (42%) CT involvement.

Multivariate analysis showed that positive SARS-CoV-2 PCR, extent of involvement on thoracic CT and time from hospital admission to antibody testing were independent predictor of positive antibody test. Analysis of patients with confirmed RT-PCR showed that age ($p = 0.047$); hospitalization ($p < 0.001$); presence of fever ($p = 0.014$) and pneumonia ($p = 0.001$); higher serum CRP ($p < 0.001$) and ferritin levels ($p < 0.001$); lower blood WBC ($p = 0.001$) and PNL counts ($p = 0.032$); moderate/severe lung involvement on thoracic CT ($p = 0.001$); need for oxygen support ($p = 0.002$); use of favipiravir ($p = 0.001$) and tocilizumab and/or anakinra ($p = 0.012$) were significantly associated with positive antibody response. Levels of D-dimer were higher and lymphocyte count were lower in patients with positive IgG antibody test but there was no significant difference between two groups. Another independent factor which was associated with antibody positively in confirmed patients was moderate/severe involvement on thoracic CT (OR 10.95, 95% CI 1.20–99.81, $p = 0.034$)

Patients with severe COVID-19 had significantly higher antibody titer compared to the patients with milder disease ($p <0.001$). Among patients with positive antibody results, patients who had received anakinra, tocilizumab or prednisolone had higher antibody titers ($p <0.05$).

In brief the lung involvement on thoracic CT was an independent predictor of antibody positively in all patients and in only confirmed case. Although receiving anti-cytokines or prednisolone were not independent predictors of antibody positivity, antibody response rate was higher in this group.

Overall, this study showed that anakinra alone or in combination with tocilizumab did not affect antibody response in COVID-19 patients because the cumulative duration of use and average dose of these drugs are the important factor which affect the adverse events and in COVID-19 infection they are used for short periods of time. Despite previous findings, these drugs did not have negative effect on antibody response.

Conclusion

Based on the reports of the investigations which were reviewed in this study, four items are important for achieving a positive effect from anakinra in patients with high level of inflammatory markers and the other sign of hyper-inflammation. These items include duration of treatment, dose of anakinra, route of administration and time of initiating of the drug. If anakinra is started with high dose (more than 100 mg) in the early phase of inflammation and around the first week of symptom onset while the patient requires oxygen supplementation but is not on invasive mechanical ventilation and for a duration of about 10 days, it might be effective and improve outcomes. Administration of corticosteroids in combination with the anakinra significantly might add to beneficial effects of anakinra. Lack of blinded studies and presence of interfering factors in the published researches prevents the authors of this review from achieving a clear conclusion about the rule of anakinra in treatment of COVID-19 patients.

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1707

1708 *Table 1: Case report of patients treated with anakinra*

	Dose	Duration (day)	Initiation time	Other drugs	Outcome
1. Feranzetti M et al(69)	100 mg SC QID	7	On day 7 of admission	**Hydroxychloroquine** 200mg TDS for 16 days **Azithromycin** 500 mg QD for 16 days **Lopinavir/ritonavir** 400/100 mg BD for 4 days **Ceftriaxone** 2g QD 7days **Piperacillin/tazobactam** 4.5 g TDS for 7 days **Linezolid** 600mg BD for 7 days	Respiratory function improved and live discharge

				Remdesivir LD200 mg 100mg QD for 7days **Enoxaparin** 4000UI QD prior to anakinra -6000UI BD with anakinra for28 days	
2. Filocamo G et al(14)	200 mg IV once followed by 100 mg SC QID	12	on day 10 of admission	**lopinavir/ritonavir** **Hydroxychloroquine** **vancomycin plus Piperacillin/ tazobactam** **cefazolin** (drugs dosing was not specified by the authors)	Respiratory improvement and live discharge from hospital
3. Kardeniz H et al(15)	100 mg SC daily	7	10 days after starting back pain (precarities)	**Hydroxychloroquine** 400mg BD first day then 200mg BD for 5days **Moxifloxacin** **Enoxaparin** 40 mg BD **Colchicine** 0.5 mg BD **Indomethacin** TDS	Live discharge from hospital and had good clinical condition

4. Kaps L et al(16)	100 mg SC daily	9 doses on over 12 days	on day 7 of admission or 12 days after symptoms onset	**Hydroxychloroquine** **Meropenem Ciprofloxacin** (Drug's dosing were not specified by the authors)	Super infection occurred but case discharge for post-acute care
5. Nemchand P et al(18)	150 mg IV BD	7	On day 9 after symptoms onset	**co-amoxiclav** IV (dosing was not specified by the authors)	Death due to thromboembolism
6. Steinhardt MJ et al(19)	2mg/kg/day (rout of administration was not specified by the authors)	5	On day 14 after symptoms onset	**Hydroxychloroquine** **Lopinavir/ritonavir** (Drug's dosing were not specified by the authors)	This dose of anakinra was sufficient to achieve effect but patient extubated and live discharge
7. Trpkov et al(20)	100 mg IV BD	5	After admission	**Dexamethasone** Single dose **Ceftriaxone** full course **Azithromycin** full course	Rapid clinical improvement, reduction in serum inflammatory markers, and a marked recovery in cardiac magnetic resonance and patient discharge from hospital
8. Samar M et al(21)	LD: 2mg/kg followed by	9	After IVIG infusion on day 17 of illnesses	**IVIG** 2g/kg/dose 2dose	Patient discharge from hospital with good general

	0.02ml/kg/hour continuous infusion			**Aspirin** 75 mg/dose QID **Dexamethasone** single dose **Methylprednisolone** 30mg/kg daily for 3 days **Piperacillin/Tazobactam** (dosing was not specified by the authors)	condition and anakinra could consider as second line therapy in pediatric patients MIS-C in context of COVID-19 infection
9. Paolera S Della et al(86)	12 mg/kg/day continuous infusion	Taper and stop after 8 days in patient 1 and 10 days in patient 2	3 days after hospital admission and 5 days after symptoms onset in patient1 and 2 days after hospital admission and 7 days after symptom onset in patient 2	**Methylprednisolone** IV 2 mg/kg/day **IVIG** IV 2g/kg 3 doses **LMWH** just in patient 2	In pediatric patients who were poor response to IVIG and glucocorticoids, anakinra could effectively improve clinical condition and patients were discharge

SC, subcutaneous; QID, four times a day; IV, intravenous; BD, two times a day; LD, loading dose.

1711 *Table 2: Case series of patients treated with anakinra*

	Dose	Duration (day)	Initiation time	Other drugs	Outcome
1. Pontali E et al (31)	100mg TDS IV for 24-48 hours then taper	Not specified by the authors	5-10 days after disease onset	**HCQ** **Enoxaparin** **Antiviral** **Azithromycin** **Methylprednisolone** in 1 patient 0.5-1mg/kg/day for 3 days (Drug's dosing were not specified by the authors)	Rapid resolution of systemic inflammation, and remarkable improvement in respiratory parameters, with reduction of oxygen support requirement. All patients live discharge
2. Aouba A et al(33)	100 mg SC BD for 3days then 100 mg daily for 8 days	11	Median 8 days (4-12) after symptoms onset	**Was not mentioned by the authors**	Inflammatory markers decrease and improve clinical condition and extension of lesions had stopped in chest CT
3. Navarro I et al(87)	100 mg SC QID was starting dose and then taper	For maximum of 19 days		**Methylprednisolone in most of the patients not all of them** 25 to 50 mg BD usually 3-4 days before starting anakinra	Early treatment was effective in patients with acute hypoxic respiratory failure for preventing from mechanical ventilation

4. George D et al(35)	200 mg IV TDS for 7days or 300 mg IV daily for 4 days and continued by 100 mg SC daily until discharge	The dose of Anakinra was 200 mg every eight hours intravenously for seven days for the Greek patients; and 300mg once daily intravenously for 4 days, followed by 100mg once daily subcutaneously until hospital discharge for the Dutch patient. The total duration of treatment with anakinra was not		**Hydroxychloroquine** in all patients except one of them **Hydrocortisone concomitantly in 3 patients** 50mg QID for 7 days IV or 250 mg IV infusion **Antibiotics (azithromycin and meropenem)** in most of the patients (Drug's dosing were not specified by the authors)	Had beneficial effects by Hscore but 3 of them have died

		specified by the authors.			
5. Celark KEN et al(36)	200 mg IV daily-BD in one patient 300 mg BD	4-21	2-24 days after symptoms onset	**Antibiotics Antifungals** (Drug's dosing were not specified by the authors)	intravenous anakinra was effective for treatment of hyperinflammation in the context of COVID-19 infection in immunosuppressed patients.
6. Villegas C et al(39)	100mg SC BD on day 1 then 100mg daily for 3 days	5		**Initial** treatment was **hydroxychloroquine** 200 mg BD + **lopinavir/ritonavir** 200/50mg BD, **corticosteroid or TCZ** 400-600 mg IV	anakinra was not effective in COVID-19 patients with hyperinflammation who have medical history of hematological malignancies

TDS, three times a day; IV, intravenous; SC, subcutaneous; BD, two times a day.

1716 *Table 3: Cohorts which used anakinra*

	Dosing	Duration (day)	Initiation time	Other drugs	Outcomes
1. Ramanathan K et al(40)	100 mg SC BD for 3 days followed by 100 mg daily for 7 days	10		**Hydroxychloroquine** 600mg daily for 10days **Azithromycin** 250 mg daily for 5 days **β-lactams Corticosteroid pulse concomitantly** (Drug's dosing were not specified by the authors)	significant reduction of mortality, along with a significant decrease in the need of mechanical invasive ventilation, with no adverse events
2. Balkhair A et al(45)	100mg SC BD for 3 days followed by 100mg SC daily max of 7 days	10		**β-lactam (ceftriaxone** 2g/day**, piperacillin-tazobactam** 4.5g TDS**)** **Macrolide (intravenous azithromycin** 500mg daily for 3 days) **Oseltamivir**	In severe COVID-19 pneumonia and high oxygen Requirement could be prevented mechanical ventilation, shortening the need for

				Enoxaparin 40 mg OD 45 **Corticosteroids** **(Dexamethasone** 6 mg IV OD or **Methylprednisolone** 40 mg IV BD for 5 days**)** **Enoxaparin (**40 mg OD**)** **IFN + KAL + RIBAV** **Hydroxychloroquine** **Tocilizumab** (These drugs dosing were not specified by the authors)	supplemental oxygen, and managing inflammation but do not reduce death
3. Kooistra EJ et al(48)	300 mg IV as loading dose followed by 100 mg IV QID	Not specified by the authors		Anakinra group compared with standard care who received **corticosteroids**, **remdesivir, chloroquine** alone or in combination	It could manage inflammation and reduce inflammatory markers but it could not reduce duration of mechanical ventilation or length of ICU stay

5. Ramanathan K et al (51)	5 mg/ kg BD as 1-hour IV infusion followed by 100 mg SC for 3 days	median duration of treatment was 9 days (IQR 7-11)		Did not received corticosteroids or immunosuppressive concomitantly **hydroxychloroquine** 200mg BD orally **lopinavir** 400mg **ritonavir** 100mg BD orally	72% of COVID-19 patients with ARDS and without mechanical ventilation were treated
6. Iglesias-juli E et al(53)	100 mg SC QID for at least 3days followed by 100 mg daily for max 7 days or gradually tapering	10	10-24 days after disease onset	Previously receive **azithromycin hydroxychloroquine** and **methylprednisolone** and the anakinra group compared with group of patients who had received **TCZ** and all of the anakinra group have received bolus of **methylprednisolone concomitant** with anakinra except one of them (drugs dosing were not specified by the authors)	Mortality was not different between two groups but adverse event has occurred in TZC group more than anakinra group and anakinra could reduce inflammatory markers more than TCZ

7. Ramanthan K et al(54)	200 mg SC BD 3 days, 100 mg BD on day 4, 100 mg once on day 5	5 or 8 (if any improvement was seen)		**Anticoagulants** **Azithromycin** **Hydroxychloroquine** **Lopinavir-ritonavir or lopinavir** **Other antivirals** **Corticosteroids (Prednisone/prednisolone, Methylprednisolone, Hydrocortisone Dexamethasone glucocorticoids)** (drugs dosing were not specified by the authors)	Could not improve outcome in patients with mild to moderate COVID-19 infection
8. Bozzi G et al(28)	200 mg SC TDS for 3 days followed by 100 mg TDS up to day 14, patients who were on mechanical ventilation received the drug	14		**Hydroxychloroquine** **lopinavir/ritonavir** **Remdesivir** in some patients **Enoxaparin** in all patients **Methylprednisolone** 1mg/kg loading dose then 0.5mg/kg in all	Anakinra in combination to methylprednisolone was independently associated with improved survival in COVID-19 patients with

	intravenously as a 3-hour infusion			intervention group of patients for 14 days which was tapered	hyperinflammation and respiratory failure even on mechanical ventilation
9. Aomar IF et al (77)	First day according to the body weight (100 mg BD-QID then 100 mg BD for day 2 to day 6	6	After receiving corticosteroid and corticosteroid plus TCZ and any improvement was not observed	**hydroxychloroquine** 800 mg/day on the first day and 400 mg/day for another 4 days **azithromycin** 500 mg on the first day and 250 mg/day for 5 days **lopinavir**/**ritonavir** 800/200 mg daily for 14 days **ceftriaxone** 2 g per day for 7–10 days **thromboembolism prophylaxis with bemiparin** at a dose adjusted according to thrombotic	Anakinra might be effective treatment in severe COVID-19 infection with moderate hyperinflammation who have received corticosteroids and corticosteroid plus TCZ and they were not effective

				risk low risk 3500 UI/day, intermediate risk 5000 IU/day	
10. de la Calle C et al(81)	100 mg SC BD on day 0 then 100 mg OD for day 1 to day 5	At least for 6 days	After receiving TCZ 13-25 days after symptoms onset	**lopinavir/ritonavir** 400/100 mg BD for 5 days **hydroxychloroquine** 400mg BD on day1 after that 200mg BD for day 2 to 5 ± **oral azithromycin**500mg for 3-5 days **SC interferon-β 0**.25mg every 48hours for 14 days **IV boluses of methylprednisolone** 0.5-1mg/kg/day for 3 days or 100-250mg for 3 days **antibiotics**	Anakinra could not be effective in patients who have received TCZ and did not improve patients clinical condition
11. Pontali E et al (84)	100 mg IV TDS for 3 days with tapering	12		**Hydroxychloroquine** 400 mg BD on the first day followed by 200-400 mg BD for 7 days and/or **azithromycin** 500 mg daily for 7 days	Using high dose of anakinra as soon as possible in hospitalized patients who require oxygen support, could

				lopinavir/ritonavir 400/100 mg BD or **darunavir/ritonavir** 800/100 mg daily for 7 days **Enoxaparin** 4000 IU/day	improve inflammatory and respiratory status in most of the cases with severe COVID-19 and improve their survival rate
12. Chowdhury J et al(79)	100 mg SC QID or 100 mg BD in renal impairment plus IVIG (0.5 g/kg/day for 3days)	7		Anakinra were compared with TCZ, all of the patients in anakinra group have received corticosteroid in contrast to TCZ group	More effective than TCZ (multivariant analysis have not shown any beneficial effect on mortality) but prompt identification and treatment of COVID-19 cytokine storm before intubation is important
13. Langer-Gould A et al(70)	100mg SC QID or 100mg SC BD in patients with renal failure	6-11		**Remdesivir** **Hydroxychloroquine** **Corticosteroids** (drugs dosing were not specified by the authors)	Patients compared with tocilizumab treated patients Prompt identification and starting treatment before

					requiring to intubation was more important than superiority of anakinra to the tocilizumab
14. Franzetti M et al (57)	100mg SC QID if managed in a regular ward, or 200 mg IV TDS if managed in the ICU	7		**Lopinavir/ritonavir** 400/100 BD **Hydroxychloroquine** 200mg BD **Antibiotics** (cefteriaxone IV 2g daily and azithromycin 500mg oral daily) **Enoxaparin** 4000IU daily (dose adjusted based on thrombotic risk and d-dimer level.)	Anakinra was effective in COVID-19 patients with ARDS and study showed that it was more evident in patients who received CPAP than in patients who received orotracheal intubation
15. Kyriazopoulou E et al(61)	100 mg SC daily	10		**Azithromycin** **Remdesivir** **Hydroxychloroquine** **Dexamethasone** (drugs dosing were not specified by the authors)	Anakinra could protect COVID-19 patients from SRF and mortality, early starting treatment using predictive biomarker suPAR was more effective

16. Della-Torre E et al(67)	5mg/kg IV BD	Until persistent clinical improvement.		**Comparator (Tocilizumab** 400-800mg IV in two doses **Sarilumab** 400mg IV single dose**)** **lopinavir/ritonavir** 400/100mg BD **Hydroxychloroquine** 500mg BD **Azithromycin** 500mg IV daily **Ceftriaxone** 2g IV daily	Treatment with biologic could significantly decrease mortality in compared to the standard care in COVID-19 patients with mild to moderate ARDS and anakinra could reduce mortality also in case of severe ARDS
17. Seniha B et al(68)	Range 100mg SC BD-200mg IV TDS	Not specified by the authors		**Favipiravir** **Hydroxychloroquine** **Tocilizumab** 400-800 mg **Prednisolone** 80mg/day for 5days **IVIG** **Convulsant plasma**	Use of anakinra, tocilizumab and prednisolone did not affect antibody response and the main role of antibody response in COVID-19 patients was extent the pulmonary involvement on CT(68)

1717

1718 *Table 4: Details of ongoing clinical investigations for anakinra*

Title	Condition	Intervention	Compared group	outcome	Allocation	Intervention Model	Masking	status
1. Anakinra, COVID-19, Cytokine Storm (SOBI)	Covid19 Cytokine Storm Mechanical Ventilation Complication	100 mg 4 times a day for 7 days	Placebo with normal saline 0.9%	Number of subjects alive without having required mechanical ventilation [Time Frame: 28 days post randomization]	Randomized	Parallel Assignment	Double (Participant, Investigator)	Not yet recruiting NCT04603742
2. A Trial Using ANAKINRA, TOCILIZUMAB Alone or in Association with RUXOLITINIB in Severe Stage 2b and 3 of COVID19-associated Disease (INFLAMMACOV)	Covi-19	Not specified	Not specified	Ventilation free days at D28 number of days living without mechanical ventilation at D28	Randomized	Parallel Assignment	None (Open Label)	Not yet recruiting NCT04424056
3. A Study in Patients With COVID-19 and Respiratory Distress Not	Covid-19	100 mg anakinra IV QID for 7 days	Standard of care	Time to recovery [Time Frame: Day 1 through Day 29]	Randomized	Parallel Assignment	None (Open Label)	Recruiting NCT04412291

Requiring Mechanical Ventilation, to Compare Standard-of-care With Anakinra and Tocilizumab Treatment the Immunomodulation-CoV Assessment (ImmCoVA) Study		Or 8mg/kg for a single infusion iv up to max 800 mg						
4. suPAR-guided Anakinra Treatment for Validation of the Risk and Management of Respiratory Failure by COVID-19 (SAVE) (SAVE)	COVID-19 Virus Diseases Corona Virus Infection Lower Respiratory Tract Infection Viral	100 mg SC daily		The ratio of patients who will develop serious respiratory failure (SRF) [Time Frame: Visit study day 14]	N/A	Single Group Assignment	None (Open Label)	Recruiting NCT04357366
5. Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome	COVID-19 Pnemonia	100 mg daily QID for max 15 days (IV)	Control arm	1.Treatment success, defined as number of patients not requiring mechanical ventilation to assess the effect of anakinra in addition to	Randomized	Parallel Assignment	None (Open Label)	Recruiting NCT04443881

Secondary to Covid-19 (ANA-COVID-GEAS) (ANA-COVID-GEAS)				standard treatment on the need for mechanical ventilation in patients with severe COVID-19 and CSS pneumonia. [Time Frame: Day 15] Treatment success, defined as number of patients not requiring mechanical ventilation by Day 15. 2.Number of patients not requiring mechanical ventilation to assess the effect of anakinra in addition to standard treatment on the need for mechanical ventilation in patients with severe COVID-19 and CSS pneumonia. [Time Frame: Day 28] Number of patients not requiring mechanical ventilation 3.Time to mechanical ventilation to assess the effect of anakinra in addition to standard treatment on the need for mechanical ventilation in patients with severe COVID-19 and CSS pneumonia. [Time Frame: Up to 28 days]				

				Time to mechanical ventilation 4.Time to oxygen saturation normalization to assess the effect of anakinra in addition to standard treatment on the need for mechanical ventilation in patients with severe COVID-19 and CSS pneumonia. [Time Frame: Up to 28 days] Time to oxygen saturation normalization 5.Stay in ICU and hospitalization to assess the effect of anakinra in addition to standard treatment on the need for mechanical ventilation in patients with severe COVID-19 and CSS pneumonia. [Time Frame: Up to 28 days] Stay in ICU and hospitalization				
6. Anakinra in the Management of COVID-19 Infection	Covid19 Pneumonia	100 mg SC BD for 3 days then 100 mg daily from	Standard of care arm	Treatment Success at day 14 [Time Frame: Day 14] Defined as WHO Clinical Progression score of ≤3	Randomized	Parallel Assignment	None (Open Label)	Recruiting NCT04643678

	Cytokine Release Syndrome	day 4 to day 7 plus Standard of Care		[Ambulatory mild disease: symptomatic; assistance needed].				
7. Assessment of Netosis During COVID-19, Under Treatment with Anakinra, an Interleukin-1 Receptor Antagonist (NET_COV)	COVID-19			Evaluation of the netosis process [Time Frame: Day 1] This outcome corresponds to the of the determination of DNA-myeloperoxidase complexes (DNA-MPO).		Cohort (Retrospective)		Recruiting NCT04594356
8. Early Treatment of Cytokine Storm Syndrome in Covid-19		100 mg SC QID for 10 days	Placebo (Normal saline)	Percentage of patients discharged from the hospital alive and without the need for mechanical ventilation. [Time Frame: Variable up to Day 28] Percentage of subjects discharged from hospital without the need for intubation and mechanical ventilation	Randomized	Parallel Assignment	Triple (Participant, Care Provider, Investigator)	Recruiting NCT04362111
9. uPAR-Guided Anakinra Treatment for Management of Severe Respiratory		Anakinra 100 mg SC daily for 10 days	placebo	Comparison of the distribution of frequencies of each score of a 5-scale patient state evaluated from the 11-point WHO Clinical Progression ordinal Scale (CPS)	Randomized	Parallel Assignment	Quadruple (Participant, Care Provider, Investigator,	Active, not recruiting NCT04680949

Failure by COVID-19 (SAVE-MORE)				between the two arms of treatment [Time Frame: 28 days]			Outcomes Assessor)	
10. Treatment of COVID-19 Patients with Anti-interleukin Drugs (COV-AID)		Rituximab Tocilizumab Anakinra (100 mg SC daily for 28 days or until hospital discharge)	Usual Care	Time to Clinical Improvement [Time Frame: at day 15] defined as the time from randomization to either an improvement of two points on a six-category ordinal scale or discharge from the hospital: Death Hospitalized, on invasive mechanical ventilation or ECMO; Hospitalized, on non-invasive ventilation or high flow oxygen devices; Hospitalized, requiring supplemental oxygen Hospitalized, not requiring supplemental oxygen Not hospitalized	Randomized	Factorial Assignment	None (Open Label)	Active, not recruiting NCT04330638

Table 5: Details of suspected investigations for anakinra

Title	Intervention	Compared group	outcome	Allocation	Intervention Model	Masking	status
SCIL-1Ra in COVID-19 Feasibility & PK/PD (SCIL_COV19)	100mg anakinra in 100mL 0.9% NaCl will be administered intravenously QID	100mg anakinra SC consistent times that are convenient and practical for the patients and research/nursing staff providing there is a minimum 8 hours and maximum 16 hours between administration	Plasma IL-1Ra levels [Time Frame: 1 week] Plasma IL-1Ra levels from Day 1 to Day 7 following administration of SC anakinra in patients with SARS-CoV-2 Plasma IL-6 levels [Time Frame: 1 week] Plasma IL-6 levels from Day 1 to Day 7 following administration of SC anakinra in patients with SARS-CoV-2	Randomized	Parallel Assignment	None (Open Label)	Suspended NCT04462757

1721 *Table 6: completed investigation but their results are not available yet*

Title	Intervention	Compared group	outcome	Allocation	Intervention Model	Masking	status
1. Efficacy of Intravenous Anakinra and Ruxolitinib During COVID-19 Inflammation (JAKINCOV)	According to clinical stage (gradual strategy): Stage 2b or 3: Anakinra 300 mg IV Overcome stage 3: Anakinra 300 mg IV and Ruxolitinib 5 mg x 2	Standard of care	Biological criteria [Time Frame: 7 days from enrolment] At least 3 parameters are met including CRP and/or Ferritin among: CRP: decrease > 50% Ferritinemia: decrease > 1/3 Serum creatinine: decrease > 1/3	Randomized	Parallel Assignment	None (Open Label)	Terminated (investigator decision) NCT04366232

			AST/ALT: decrease > 50% Eosinophils > 50 /mm3 Lymphocytes > 1000 /mm3				
2. Anakinra for COVID-19 Respiratory Symptoms (ANACONDA)	Anakinra 400mg IV from Day 1 to Day 3 (two injections of 100 mg each 12 hours) and 200mg the remaining 7 days. The total duration of Anakinra is 10 Days.	Standard of care	Treatment success [Time Frame: After 14 days of treatment] The primary endpoint is treatment success at Day 14, defined as a patient alive and not requiring any of the following: Invasive mechanical ventilation (IMV) or	Randomized	Parallel Assignment	None (Open Label)	Terminated (Efficiency and safety reasons) NCT04364009

			Extracorporeal membrane oxygenation (ECMO).				
3. Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection.	Emapalumab Anakinra: IV infusion QID for 15 days. 400 mg/day in total, divided into 4 doses given every 6 hours	Standard of care	Treatment success [Time Frame: Up to Day 15] Defined as the proportion of patients not requiring invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO)	Randomized	Parallel Assignment	None (Open Label)	Terminated NCT04324021

4. CORIMUNO-ANA: Trial Evaluating Efficacy of Anakinra In Patients with Covid-19 Infection (CORIMUNO -ANA)	Treatment includes the administration of Two IV infusions / day of ANAKINRA 200mg (Total 400 mg) at day 1 (D1), D2 and D3, two IV infusions / day of ANAKINRA 100mg (Total 200 mg) at day 4 (D4), and one IV infusion of ANAKINRA 100mg (Total 100 mg) at day 5 (D5).	Standard of care	Survival without needs of ventilator utilization at day 14 [Time Frame: 14 days] Survival without needs of ventilator utilization (including non-invasive ventilation and high flow) at day 14. Thus, events considered are needing ventilator utilization (including Non-Invasive Ventilation, NIV or high flow), or death.				

			New DNR order (if given after the inclusion of the patient) will be considered as an event at the date of the DNR. WHO progression scale ≤ 5 [Time Frame: 4 days] Proportion of patients alive without non-invasive ventilation of high low at day 4 (WHO progression scale ≤ 5). A patient with new DNR order				

			at day 4 will be considered as with a score > 5. Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) or withdrawal of NIV or high flow (for > 48h), at day 14 [Time Frame: 14 days] Cumulative incidence of successful tracheal extubation (defined				

			as duration extubation > 48h) at day 14 if patients have been intubated before day 14; or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Death or new DNR order (if given after the inclusion of the patient) will be considered as a competing event.				

			Decrease of at least one point in WHO progression scale score [Time Frame: 4 days] Proportion of patients with a decrease of WHO score of at least 1 point at day 4				

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