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Editorial

Editorial-An Update on Management of Severe COVID19 Presenting with Cytokine Release Syndrome Responsible for Most Mortalities in COVID19

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After having reviewed the structural details of covid 19 virus and presentation we updated on the newer insight on the virus with regard to effective therapy. Simultaneously we tried to update on the pathophysiology with HAPE hypothesis needing changes in approach regarding no immediate intubation and rather preferable ventilation with O2 alone [1,2]. Further we emphasized on regards to cytokine release syndrome (CRS) development and thrombosis development in etiopathogenesis of severe acute respiratory distress syndrome (ARDS) along with management during pregnancy and lactation [3]. Considering the numbers are still increasing worldwide with USA numbers over 2 million and Indian number increasing to over 4 lac and Pakistani to 1.75 lacs with over 4500 cases in Pakistan along with Mexico in 24 hrs since no vaccine still available (Table 1) we have decided to update on the management of severely ill cases here. Here we are stressing on how to use various IL-6 inhibitors like tocilizumab. CRS is the leading cause of serious morbidity in patients infected with SARS-CoV and MERS-CoV. Elevated serum Interleukin (IL)-6 levels have been found in patients with SARS-CoV-1, with which SARS-CoV-2 is closely linked, and are associated with respiratory failure, ARDS, and poor clinical outcome [4-6]. It has been estimated that 20% of COVID-19 patients will have severe symptoms of pneumonia, leading to ARDS [7,8]. This complication is similar to the ARDS caused by the release of cytokines and the Haemophagocytic LymphoHistiocytosis Syndrome (HLHS) previously observed in patients with SARS-CoV and MERS-CoV as well as patients with B acute lymphoblastic leukemia receiving genetically modified autologous T-lymphocytes (CAR-T cells). The first COVID-19 pathology observed bilateral diffuse alveolar injury with cytomyxoid fibroma exudate, and subsequent peripheral flow cytometry analysis found a decrease in CD4+ and CD8T-cells but an increase in the Th17 cell proportion [9]. Th17 cells are helper T-cells differentiated from Th0 cells mainly stimulated by interleukin-6 (IL-6) and IL-23 [10]. A study to be published including 40 COVID-19 patients (of whom 13 were severe) suggests that severe cases show a sustained decrease in the proportion of lymphocytes compared with mild cases. In addition, CD8 +T-cells decreased and inflammatory cytokines [IL-6, IL-10, IL-2 and interferon-gamma (IFN γ)] in the peripheral blood increased in severe cases. Taken together, we have a reasonable hy-

Country	Total Cases	New Cases	New Deaths	Total Recovered	Active Cases
World	89220723	+13,518	+5258	4,743,658	3,711,544
USA	2330578		+1373	972,941	1,235,657
Brazil	1070139		+621	543,186	476,895
Russia	576,952		+542	334,592	234,358
India	411,773	+46	+4	228,307	234,358
UK	303,110			N/A	N/A
Spain	293,018			N/A	N/A
Peru	251,338			7,861	138,763
Italy	238,275			182,453	21,212
Chile	236,748			196,609	35,844
Iran	202,584		9507	161,384	31,693
Germany	191,216		+ 147	174,700	7555
Turkey	186,493			158,828	22,738
Pakistan	176,617	+4951	+119	67,892	105,224
Mexico	175,202	+20,781	+387	131,686	22,735
Russia	8672	+1175	+5	580	8029
Sweden	8419	+726	+96	205	7527
Norway	6086		+12	32	5953
India	5745	+298	+18	506	5065

Table 1: Worldwide epidemiology as on 21/6/2020 at 11.30 pm.

pothesis that cytokine storms play an important role in severe COVID-19 cases. Therefore, neutralising key inflammatory factors in CRS will be of great value in reducing mortality in severe cases (See figure 1 and 2) for highlighting CRS. Hypergammaglobulinemia, myocardial myxoma, bladder cancer and chronic rheumatoid arthritis (RA), among others, are accompanied by abnormally increased levels of IL-6. Participate in the occurrence and development of cardiovascular diseases (CVD) [11]. Myocardial ischaemia, coronary atherosclerosis, angina pectoris, congestive heart failure and hypertension, among others, are accompanied by abnormally increased IL-6 levels. Role of Interleukin-6 receptor antagonist- tocilizumab- The classical IL-6 signal is limited to cells (macrophages, neutrophils, T-cells, etc.) that express the IL-6R and plays a leading role in the low level of IL-6. The combination of IL-6 and cell related IL-6R leads to gp130 homologous dimerisation and initiates downstream pathways. However, when the level of IL-6 increases, the IL-6 signal is widely expressed because gp130 is ubiquitous. Binding of tocilizumab to cell-related IL-6R and sIL-6R can inhibit classical and trans signals. Thus, it can inhibit CRS. Tocilizumab is a recombinant humanised anti-human IL-6R monoclonal antibody of the IgG1 subtype. Tocilizumab specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R andmIL-6R) and inhibits sIL-6R- and mIL-6R-mediated signal transduction. It has been approved for the treatment of RA and systemic juvenile idiopathic arthritis. In addition, it has also been reported to play a role in Castleman disease, and Crohn's disease. It is worth noting that tocilizumab is effective in the treatment of patients with severe CRS [12,13] (Figure 1 and 2). The recommended dose of tocilizumab is 8 mg/kg by intravenous (i.v.) drip every 4 weeks for adult with RA, which can be used in combination with methotrexate or other antirheumatic drugs. When liver enzyme abnormalities occur or the neutrophil or platelet counts decrease, the dose of tocilizumab can be reduced to 4 mg/kg. For systemic juvenile idiopathic arthritis, the dose of tocilizumab is 12 mg/kg (for body weight < 30 kg) or 8 mg/kg (for body weight ≥ 30 kg). An i.v. drip every 2 weeks is recommended, with an infusion time of > 1h. The safety of tocilizumab was studied in five phase III double blind controlled trials and its extended period (data come from the treatment of RA) [14]. The total control population included all patients in the double-blind period of each core study from randomised grouping to the first change of treatment regimen, or the completion of a 2-year treatment period. Among them, the double-blind control period of four studies was 6 months, and the other double-blind control period was 2 years. In these double-blind controlled trials, 774 patients received tocilizumab 4 mg/kg combined with methotrexate (MTX) and 1870 patients received with tocilizumab 8 mg/kg combined with MTX or other disease-modifying antirheumatic drugs (DMARDs). A total of 288 patients were treated with tocilizumab 8 mg/kg alone. In a 6-month controlled trial, the incidence of infection events in patients receiving tocilizumab 8 mg/kg + DMARD or placebo + DMARD was 127 cases/100 patient-years and 112 cases/100 patient-years, respectively. Among the total exposed population, the overall incidence of infection events in the tocilizumab + DMARD group was 108 cases/100 patient-years. The 6-month controlled trial also showed that the incidence of severe infection (bacteria, viruses and fungi) in the 8 mg/kg + DMARD group was 5.3/100 patient-yrs, whilst that in the placebo + DMARD group was 3. 9/100 patient yrs. In the monotherapy trial, the incidence of severe infection was 3.6 cases/100 patient-yrs in the tocilizumab group and 1.5 cases/100 patient-yrs in the MTX group. Regarding the safety of tocilizumab in the treatment of patients with severe COVID-19, a recent study included 21 patients with a mean age of 56.8 ± 16.5 yrs (range 25 - 88 yrs) [15]. There were no complications associated with tocilizumab treatment and no history of illness deterioration or death. Overall, the risk of secondary infection with tocilizumab is not too high. The largest clinical data from China's Centers for Disease Control and Prevention show that of the 44,672 confirmed cases included, 2683 (12.8%) had hypertension, 1102 (5.3%) had diabetes mellitus (DM) and 873 (4.3%) had other CVD [16]. A total of 1023 deaths (2.3%) occurred among confirmed cases; the crude death rate with no reported complications was 0.9% whereas the mortality rate of patients with complications was much higher (10.5% of patients with CVD, 7.3% of patients with DM and 6.0% of patients with hypertension). There is some controversy about whether tocilizumab increases the risk of CVD. Data from several randomised controlled trials (RCTs) and real-world evidence (RWE) studies have been published. A study by Giles., et al. included 3080 patients aged > 50 yrs with more than one risk factor for CVD who met the diagnosis of active RA, of whom 1538 were treated with tocilizumab and 1542 were treated with etanercept [17]. After an average follow-up of 3.2 years, 83 major adverse cardiovascular events (MACEs) occurred in the tocilizumab group (5.4%), whilst 78 MACEs occurred in the etanercept group (5.1%). The resulting hazard ratio (HR) was 1.05 [95% confidence interval (CI) 0.77 - 1.43]. The authors concluded that tocilizumab had a higher cardiovascular risk than etanercept. Interestingly, two RWE studies came to a different conclusion from the above RCT. In the study by Kim., et al. cardiovascular events in RA patients newly initiating tocilizumab or tumour necrosis factor inhibitors (TNFi) were compared; after strict propensity score matching, 9218 tocilizumab initiators and 18810 TNFi initiators were included [18]. The incidence rate of cardiovascular events

was 0.52 per/100 person-years for tocilizumab and 0.59 per/100 person-years for TNFi. The combined HR was 0.84 (95% CI 0.56 - 1.26). Another RWE study by Xie., et al. [19], came to a similar conclusion that there was no significant difference in the risk of cardiovascular events associated with the use of tocilizumab compared with TNFi [HR (Medicare database) = 0.79 (95% CI 0.65 - 0.96); HR (Market Scan database) = 0.84 (95% CI 0.52 - 1.37)]. Although the conclusion of the RCT study was slightly different from RWE studies, the 95% CIs of all studies were not significant (i.e. the 95% CI contains 1), so there is insufficient evidence to conclude that tocilizumab increases cardiovascular events. In August 2017, the US Food and Drug Administration (FDA) approved tocilizumab for the treatment of CRS caused by chimeric antigen receptor T-cell (CAR-T) immunotherapy. A 7-year-oldgirl with acute lymphoblastic leukaemia (ALL) developed a severe CKS following CAR-T treatment. Subsequent treatment with tocilizumab dramatically improved her condition and did not affect the efficacy of CAR-T. Another study reported that a male patient with ALL developed HLHS following treatment with blinatumomab. The patient developed ARDS and methemoglobinemia. Subsequent treatment with tocilizumab successfully saved the patient's life.

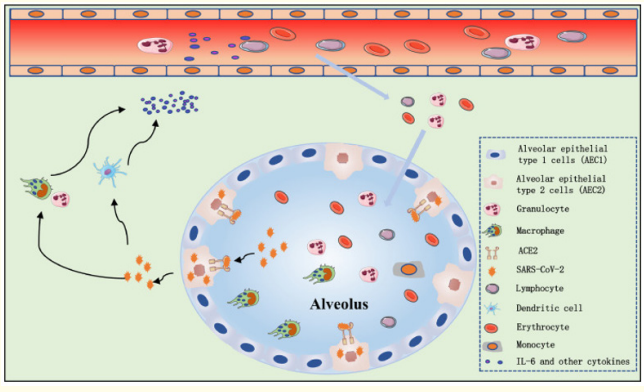

Figure 1: Courtesy ref no-20-Possible mechanism of cytokine release syndrome in severe coronavirus disease 2019 (COVID-19) patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects alveolar epithelial cells [mainly alveolar epithelial type 2 (AEC2) cells] through the angiotensin-converting enzyme 2 (ACE2) receptor. Destruction of epithelial cells and the increase of cell permeability lead to release of the virus. SARS-CoV-2 activates the innate immune system; macrophages and other innate immune cells not only capture the virus but also release a large number of cytokines and chemokines, including interleukin-6 (IL-6). Adaptive immunity is also activated by antigen-presenting cells (mainly dendritic cells). T- and B-cells not only play an antiviral role but also directly or indirectly promote the secretion of inflammatory cytokines. In addition, under the stimulation of inflammatory factors, a large number of inflammatory exudates and erythrocytes enter the alveoli, resulting in dyspnoea and respiratory failure.

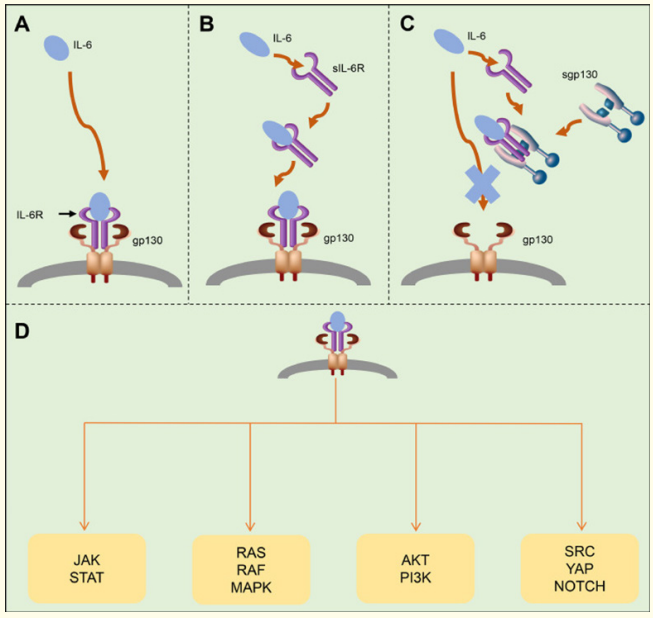

Figure 2: Courtesy ref no-20-Signal transduction pathways of interleukin-6 (IL-6): (A) classical signal transduction; (B) trans signal transduction; and (C) trans-presentation. (D) The next step is to activate the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway (STAT1, STAT3 and, to a lesser extent, STAT5); in addition, the RAS-RAF, SRC-YAP-NOTCH and AKT-PI3K pathways are also activated. These promote complex biological functions such as proliferation, differentiation, oxidative stress and immune regulation, etc. IL-6R, interleukin-6 receptor; gp130, glycoprotein 130; sIL-6R, soluble interleukin-6 receptor; sgp130, soluble glycoprotein 130.

SARS-CoV-2, SARS-CoV and MERS-CoV are coronaviruses and CRS of varying degrees has occurred in severe patients with SARS and MERS. All of them had high expression of IL-6. Currently, a clinical trial in China with a small sample size (Chinese Clinical Trial Registry ID: ChiCTR2000029765; http://www.chictr.org.cn/showprojen.aspx?proj=49409) has shown good efficacy of tocilizumab. All 21 patients included met the criteria for severe or critical COVID-19, including one of the following: shortness of breath;

respiratory rate > 30 bpm; oxygen saturation < 93% while resting; or PaO2/FiO2 ratio ≤ 300 mmHg. Critical criteria included one of the following: respiratory failure requiring mechanical ventilation; shock and admission to the ICU with other organ failure. After a few days of treatment, the body temperature of patients with fever (all 21 patients initially had a fever) returned to normal and all other symptoms were significantly improved. Of 20 patients, 15 (75%) had reduced their oxygen intake and 1 patient did not require oxygen. Imaging examination by CT showed that 90. 5% (19/21) of the patients had absorption of pulmonary lesions. Laboratory examination showed that the proportion of peripheral blood lymphocyte and CRP returned to normal. An inadequacy of the study is that only the level of IL-6 in peripheral blood before treatment with tocilizumab was reported (mean value 132.38 ± 278.54 pg/mL), but the level of IL-6 after treatment was not. Finally, from analysis of the possible mechanism of COVID-19 and small sample clinical data, tocilizumab has good efficacy. From a pharmacoeconomic viewpoint, we suggest that it should be used in critically ill COVID-19 patients with significantly elevated IL-6. In conclusion, CRS occurs in a large number of patients with severe COVID-19, which is an important cause of death. IL-6 is the key molecule of CRS, therefore the IL-6R antagonist tocilizumab may be an important drug to save patients' lives [20]. Role of immunomodulation therapies with interleukin-1 receptor antagonist (Anakinra). Dimopoulos., et al. [21] describe eight cases ofCOVID-19 pneumonia patients who all had secondary hemophagocytic Lymphohistiocytosis (HLHS) and showed favorable responses in respiratory function upon treatment with the interleukin-1 receptor antagonist (Anakinra). Anakinra treatment was delivered to 8 severe COVID-19 patients All patients had secondary HLHS - Respiratory function was improved at the end of treatment (Figure 3). In one patient, the need for mechanical ventilation was prevented. Dysregulation of inflammation is hypothesized to play a crucial role in the severe complications of COVID-19, with the IL-1/IL-6 pathway being central. 7 were hospitalized in intensive care units (ICUs) in Greece and one non-ICU patient in the Netherlands-with the interleukin-1 receptor antagonist Anakinra. All patients scored positive for the hemophagocytosis score (HScore) and were diagnosed with secondary hemophagocytic lymphohistocytosis (sHLH) characterized by pancytopenia, hyper-coagulation, acute kidney injury, and hepatobiliary dysfunction (Figure 3). At the end of treatment, ICU patients had less need for vasopressors, significantly improved respiratory function, and lower HScore. Although three patients died, the mortality was lower than historical series of patients with sHLH in sepsis. These data suggest that administration of Anakinra may be beneficial for treating severe COVID-19 patients with sHLH as determined by the HScore, and they support the need for larger clinical studies to validate this concept. The most fearsome complication of pneumonia caused by the novel coronavirus SARS-Cov-2 (COVID-19 illness) is severe respiratory failure leading to mechanical ventilation (MV). The mortality in patients with severe COVID-19 admitted in the intensive care units is reported to be between 50% and 65%. The cytokine storm described in these patients [21] introduced the concept of attenuation of the hyperinflammation, with agents targeting pro-inflammatory cytokines, mainly interleukin (IL)-1b and IL-6. Several clinical trials on the efficacy of Anakinra, which targets IL-1b and of Tocilizumab, Siltuximab, and Sarilumab, which target the IL-6 pathway, are ongoing. Overproduction of IL-1b by tissue macrophages triggers secondary.

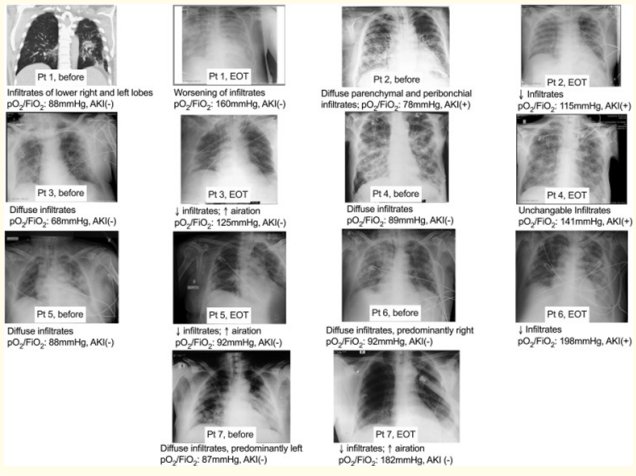

Figure 3: Courtesy reference number -21-Comparative Chest X-rays of the Seven Greek Patients Necessitating Mechanical Ventilation on Day 1 before Start of Anakinra and at the End of Treatment (EOT) with Anakinra. Below each X-ray a brief diagnosis is provided along with the ratio of the partial oxygen pressure to the fraction of inspired oxygen (pO2/FiO2) of that day. The presence (+) or absence (−) of acute kidney injury (AKI) is also noted. Abbreviations: ↓: Decrease; ↑: Increase.

In sepsis, sHLH is a complication leading independently to early death in the first 10 days [21]; 28-day mortality is reaching 67%. Administration of Anakinra, which is a recombinant soluble receptor antagonist of IL-1b and IL-1a, in patients with signs of sHLH reduced mortality by 30% [21]. Desirable outcomes would be that tocilizumab reduces the number of days that patients are dependent

on mechanical ventilation and reduces the invasiveness of breathing assistance. Furthermore, this treatment might result in fewer admissions to intensive care units. Next to these efficacy parameters, safety of a therapy with Tocilizumab in COVID-19 patients has to be monitored closely, since immunosuppression could lead to an increased rate of bacterial infections, which could negatively influence the patient's outcome. Multicentre, prospective, 2-arm randomised (ratio 1:1), double blind, placebo-controlled trial with parallel group design. Inclusion criteria: 1. Proof of SARS-CoV2 (Symptoms and positive polymerase chain reaction (PCR)). 2. Severe respiratory failure: a. Ambient air SpO2 ≤ 92% orb. Need of ≥ 6l O2/min orc. NIV (non-invasive ventilation) ord. IMV (invasive mechanical ventilation). 3. Age ≥ 18 years. Exclusion criteria: 1. Non-invasive or invasive mechanical ventilation ≥ 48 hours. 2. Pregnancy or breast feeding. 3. Liver injury or failure (AST/ALT ≥ 5x ULN). 4. Leukocytes < 2 × 103/µl. 5. Thrombocytes < 50 X 103/µl. 6. Severe bacterial infection (PCT > 3 ng/ml). 7. Acute or chronic diverticulitis. 8. Immunosuppressive therapy (e.g. mycophenolate, azathioprine, methotrexate, biologicals, prednisolone > 10 mg/d; exceptions are: prednisolone ≤ 10 mg/d, sulfasalazine or hydroxychloroquine). 9. Known active or chronic tuberculosis. 10. Known active or chronic viral hepatitis. 11. Known allergic reactions to tocilizumab or its ingredients. 12. Life expectation of less than 1 year (independent of COVID-19). 13. Participation in any other interventional clinical trial within the last 30 days before the start of this trial. 14. Simultaneous participation in other interventional trials (except for participation in COVID-19 trials) which could interfere with this trial; simultaneous participation in registry and diagnostic trials is allowed. 15. Failure to use one of the following safe methods of contraception: female condoms, diaphragm or coil, each used in combination with spermicides; intra-uterine device; hormonal contraception in combination with a mechanical method of contraception. The data collection of the primary follow up (28 days after randomisation) takes place during the hospital stay. Subsequently, a telephone interview on the quality of life is conducted after 6 and 12 months. Participants will be recruited from inpatients at ten medical centres in Germany. Intervention arm: Application of 8 mg/kg body weight (BW) Tocilizumab i.v. once immediately after randomisation (12 mg/kg for patients with < 30 kg BW; total dose should not exceed 800 mg) and conventional treatment. Control arm: Placebo (NaCl) i. v. once immediately after randomisation and conventional treatment. Primary endpoint is the number of ventilator free days (d) (VFD) in the first 28 days after randomisation. Non-invasive ventilation (NIV), Invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO) are defined as ventilator days. VFD's are counted as zero if the patient dies within the first 28 days the randomisation code will be generated by the CTU (Clinical Trials Unit, ZKS Freiburg) using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Randomisation will be stratified by centre and will be performed in blocks of variable length in a ratio of 1:1 within each centre. The block lengths will be documented separately and will not be disclosed to the investigators. The randomisation code will be produced by validated programs based on the Statistical Analysis System (SAS). Maes., et al. presented a structured summary for 16 Belgian ptdsw in ICUTO BE Randomized in 5 experimental arms i) Anakinra alone ii) Siltuximab alone (anti IL-6 chimeric Antibody) iii) a combination of Siltuximab along with Anakinraiv) Tocilizumab alone v) combination of Tocilizumab along with Anakinra besides standard care. Anakinra users will get s/c 100 mg for max of 28 days or hospital discharge whatever is 1st Siltuximab is 11 mg/kg or Tocilizumab 8 mg/kg as single iv injection. Primary end point is clinical improvement Further Gorman., et al. is trying an RCT on mesenchymal stromal cell in ARDS related to severe COVID19.

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