

ROLE OF TOCILIZUMAB IN FIGHTING COVID 19

ABSTRACT

BACKGROUND: Tocilizumab is the repurposed drug used in the severely ill COVID-19 patients. A lot of traction has gain over the drug but more studies are awaited to ensure the efficacy of the drug with proper backing from empirical data. Tocilizumab, a drug which is used in treatment of rheumatoid arthritis suddenly came into limelight when it got listed as drugs used for the treatment of COVID-19 patients. As earlier discussed, many existing drugs which were already in use for treating other ailments were being tested if they are suitable to treat COVID-19 disease. **Tocilizumab have** the anti-inflammatory properties which were in particular were useful in COVID-19 which creates an inflammation all across the organs.

SUMMARY: COVID-19 is the novel disease outbreak later progressed into deadly pandemic has presented the huge challenge to contain it clinically as no drug was available prior the outbreak of the disease. Vast amount of drugs can be used to at least suppress the viral spread which was found to be true. Although it was not hundred percent foolproof but it was an emergency situation and various drugs were used according to local ground conditions and patients response to the drug along with age and severity of the illness. Tocilizumab was one such drug which was repurposed for the treatment of COVID-19 patients. Many drugs such as Hydroxychloroquine (HCQ), Tocilizumab were repurposed from their existing use. Tocilizumab is currently used in the treatment of rheumatoid arthritis. Various studies have shown the efficacy of the drug among the severely ill COVID-19 patients which ranges up to 66 percent. In certain cases worsening of the existing medical condition has been observed.

CONCLUSION: Vaccine nationalism must be set aside and low and middle income countries where most of the population of the world resides, should be vaccinated as even one case can culminate into another disaster as was seen during highly contagious COVID-19. More empirical data is needed from across the globe to ensure the assessment of the efficacy of the drug. Also certain cases of shortage of the said drug for non-COVID-19 purpose also looked into seriously has it can create a parallel disaster.

KEYWORDS: Tocilizumab, COVID-19, Vaccine, HCQ, preventive measures, social vaccine.

Should be explained methods in the study especially in abstract section (method in the review study)

INTRODUCTION:

Coronavirus disease 2019 or COVID-19 is ongoing deadly pandemic which is persisting for around 2 years.(1)It all started from Wuhan city of the Hubei province in China where first instances of COVID-19 occurred.(2) It spread throughout the world as countries were late to acknowledge the highly contagious nature of the viral disease. The pandemic is so devastating

that no other disease outbreak or manmade disaster has culminated to such a fatal level. As of September 30, 2021, 233,434,862 infections due to novel coronavirus have been reported and 4,777,272 case fatalities attached to the same. Till date 6,220,064,129(3) number of vaccines has been administered but the number is rising daily with ground breaking efforts by highly populated countries like India where daily vaccine inoculation reached to a peak of 20 million jabs a day(4). But many people are still far from getting their first jab against the mandated two jabs of various vaccines. Many candidates are in line to get approved from drug controller agencies of various nations. As the pandemic was new and no precedent is available regarding the disease, no drug was readily available to contain the pandemic at the initial level. Non-pharmacological interventions such as lockdowns were used to curb the spread but it temporarily contained it. Another option of repurposing the existing drug among which Tocilizumab was one of the popular drugs. It gained traction when several studies carried out in different parts of the world conveyed the positive response about the administration of drugs in severely ill patients. Of course the drug is not made solely for the treatment of COVID-19 and has its limitations. Preventive measures are the effective way to deal with the pandemic situation. Along with vaccination, wearing of masks and maintaining physical distancing are advised and previously proven measures which can be undertaken through people's participation.

REPURPOSING EXISTING DRUGS

The Coronavirus disease 2019 struck the world with a shock. The COVID-19 as it is abbreviated is the rapidly mutating and spreading viral disease which is wreaking havoc all over the world. This is an unprecedented outbreak of the disease which was soon upgraded to pandemic status citing its pan-globe effect. Millions of people succumbed to the viral disease which exploits mostly the existing immune deficient condition in the person although if the viral load is high then it can severely affect the patients who had no medical history of any chronic disease. In this fight against COVID-19, the main weapon of countering drug was absent as the viral infection was new to the researchers and scientific community. Considerable amount of time is needed to develop an all-encompassing drug to be manufactured which is still out of bound from the humanity(5). Although vaccines are out and millions of people are being inoculated, the chance of reinfection and mutation in the virus which can evade the vaccine should be the major cause of concern. The constant observation by researchers has already suggested that there is major mutation which can circumvent the vaccine protection and infect the individual. Therefore it is extremely important to have an established treatment protocol which can guide the due course of treatment. But it was absent due to the novelty of the disease and therefore scientists and researchers had to think the way out of the rapidly expanding disease. One advantage of the situation of the coronavirus disease 2019 was its lineage and resemblance to the previous outbreaks of coronaviruses which was recorded in 2003 and 2012 in different parts of the world(6). This excited the scientists and researchers as there was basic information available and they did not need to begin from the scratch. Many observations were already in record and scientists need to do genome sequencing of the novel coronavirus so they can be precise and up to date. This opens the case for repurposing the existing available drugs which are already in use for some other ailments(7). Vast amount of drugs can be used to at least suppress the viral spread which was found to be true. Although it was not hundred percent foolproof but it was an emergency situation and various drugs were used according to local ground conditions and patients response

to the drug along with age and severity of the illness. Tocilizumab was one such drug which was repurposed for the treatment of COVID-19 patients.

TOCILIZUMAB

Tocilizumab is an immunosuppressive drug which is mainly used in the medical condition of rheumatoid arthritis and systemic juvenile idiopathic arthritis. Rheumatoid arthritis is the commonly occurring condition among old age patients and it shows swollen and painful joints which becomes stiff post resting duration. It is used against the Interleukin-6 receptor as the monoclonal antibody derived from non-human source and which is humanized in the due course of production. Tocilizumab is found to be lowering the IL-6 which is necessary in many cases as the body overkill the healthy cell along with the bad cells which can escalate in to organ failure. Tocilizumab is also used in other medical condition like giant or temporal cell arteritis, neuromyelitis optica, Castleman's disease (enlargement of lymph node tissue), cytokine release syndrome(8).

TOCILIZUMAB IN COVID-19

Tocilizumab, a drug which is used in treatment of rheumatoid arthritis suddenly came into limelight when it got listed as drugs used for the treatment of COVID-19 patients. As earlier discussed, many existing drugs which were already in use for treating other ailments were being tested if they are suitable to treat COVID-19 disease. Tocilizumab have the anti-inflammatory properties which were in particular were useful in COVID-19 which creates an inflammation all across the organs(9). In some patients the acute respiratory distress syndrome (ARDS) which created complications in COVID-19 patients such hyper inflammation were bound to slip in pneumonic condition. Pneumonia in COVID-19 patients is a life threatening condition which needs to be treated on urgent basis. In one instance of study on the COVID-19 patients affected by ARDS and subsequently to pneumonia in Italy, **Tocilizumab** has shown promising results. Tocilizumab was administered intravenously two shots, 12 hours apart and third shot was discretionary which was to be administered according to the condition of the patient. Ventilator support was required to all the studied patients proper to the administration of the drug. Patients were monitored and graded using BRESCIA scale for the severity of COVID-19 or coronavirus disease 2019. It ranges from 0 to 8 where 0 indicates least severe condition of COVID-19 where only monitoring of saturated level of oxygen is required while 8 indicates highest level of complexity and multiple emergency situation regarding patients. Tocilizumab is considered fit for the patients of BRESCIA scale 3 to 8 with varying amount of dosage administered along with certain other listed drugs. Respiratory failure post pneumonia is the common condition seen among COVID-19 patients but reason behind it is not yet clear. Total 100 patients were observed and studied out of which 88 were male and 12 were female. 66 male and 11 female shown improvement post administration of **Tocilizumab** which accounts to 77 percent of the total pool while 23 patients were showing either worsening of condition or shown fatal clinical outcome. 66 percent that is 66 patients had on or the other underlying medical illness also known as comorbidity. 46 percent of the total pool were suffering from arterial hypertension. Obesity was found in 31 percent of the patients. Hypertension and obesity was among the most observed comorbidity among COVID-19 patients and chances of developing severe clinical complication

are greater among this section of population making them extremely vulnerable to produce fatal clinical outcome(10). BCRSS score for the recovered patient was 3 to 7 prior to the administration of COVID-19 while it came down drastically to 1 – 3 post administration of the said drug. Tocilizumab was administered 8 milligram per kilogram of the patient's weight and maximum amount was capped at 800mg. It was spaced apart by 12 hours administered two separate dosage. Third dose which was optional was to be administered after 24 hours of administration of second dose. Preliminary results of the study are positive regarding the administration of the **Tocilizumab** as just after the administration of the first dose, majority of the patients showed improvements. The study also suggests that considering rapid spread of the disease and deaths due to respiratory distress and pneumonia, administration of Tocilizumab can offer some relief in grim situation. Although more cohort studies are needed across the globe to ensure precise and accurate outcome of the study(8).

Among monoclonal antibodies therapy **Tocilizumab** is one of the widely used therapies. It act against the Interleukin-6 (IL-6) which helps decreasing the severity of the disease. IL-6 is the cytokine which is responsible for the inflammatory and immunity response. It is basically a polypeptide which plays key role in bodily functions like metabolism, acute inflammation and immune response. Auto immune cell differentiation and so on. It is behind the cytokine release syndrome. A life threatening condition can be created due to IL-6 excess response which can culminate into multi organ damage. Coagulation has been also seen among Patients of COVID-19 which is primarily due to elevated levels of COVID-19. A study was conducted in China in the Hospital of Wuhan. 15 patients were included in the study which consisted of 03 females and 12 males. The patients were aged ranging from 62 to 80 years 73 being the median age. 7 patients were critically ill which constituted roughly about 46 percent of the pool while 6 of them were moderately ill. 10 of the total 15 patients were studied were having different comorbidities. The dose administered was ranging from 80 to 600 mg per time per person. The laboratory analysis of the patients suggested that all the patients were showing elevated levels of CRP levels which were relived after the administration of the Tocilizumab in most of the patients(11). The relief feature of **Tocilizumab** in inflammation and hyper inflammation were found to be of no use in 4 patients out of which 3 showed fatal clinical outcome and one showed worsening of condition post administration of TCZ. Rest of 11 patients were back to normal levels of CRP levels post treatment within one week. The indication of TCZ use is the elevated levels of IL-6. According to the laboratory data, the IL-6 levels were as high as 627 pg/ml which is almost 90 times higher than normal levels of IL-6. After the therapeutic intervention of TCZ, it dropped to manageable levels in 10 patients. The cytokine storm which engulfs the good cell in pursuit of killing bad or rogue cell in the body has been found to be successfully treated with TCZ. TCZ along with methyl prednisolone, corticosteroids were given as a combination drug which were found to be successful in relieving the patient from severe clinical condition. Previously to control the cytokine storm, which is a hyper immune response of the body, corticosteroids such as dexamethasone and methyl prednisolone were administered which rendered the COVID-19 patients with extremely low immune system power. Which further created lots of side effects which were a whole new emergency. The main side effects were fungal infection which was amplified by the humid and dirty surrounding condition around the Intensive Care Unit due to huge and rapid influx of patients. Black fungus was the prominent fungus which spreads through nose and jaw to eye region. In some cases patients made to lose one eye to stop the fungal infection from spreading further. The fatality was also reported in most cases due to transmission of infection to the brain region. The case fatality rate (CFR) due to black fungus was 50 to 70

percent which was huge. Hypertension is the most common comorbidity seen among severely ill patients of COVID-19(12).

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LIMITATIONS OF USING TOCILIZUMAB

Although **Tocilizumab** can be considered as successful drug while treating many severe COVID-19 patients, the **Tocilizumab** is not the medical therapy solely made for the COVID-19 treatment, it has certain limitations regarding use as drug for treating COVID-19 patients. IL-6, CRP and D-dimer are some of the parameters that are being used to administer the repurposed drugs. But there are certain parameters which are out of bound of these three parameters. Therefore we cannot use the TCZ in such cases. Also TCZ is originally a drug used to treat the rheumatoid arthritis. The over increasing demand is hampering the efforts to contain or treat the rheumatoid arthritis which is also prevalent among old age population and among widespread occurring ailment. Not enough study has been done to pin point the target group where TCZ can be used so that there is minimal collateral damage or side effects(13).

COMORBIDITY AND COVID-19....how are correlation with

Comorbidity is the underlying medical illness along with other medical conditions. Coronavirus disease 2019 or COVID-19 made the word widespread as comorbid patients have to face severe repercussions if they get contracted by COVID-19. From the evidence and research available so far comorbid patients are highly susceptible to develop a severe and fatal clinical outcome. In fact majority of the case fatalities are the result of combination of COVID-19 and comorbidities. Several comorbidities are widespread across the globe such as hypertension, diabetes mellitus, asthma, bronchial; infections, liver cirrhosis, obesity, cardiovascular diseases, renal ailments and so on which makes the patient weak and vulnerable to catch such infection as COVID-19(14). The comorbid patient are in immunosuppressive state where the immune system is not responding at full potential. Hence infection such as COVID-19 can spread and mutate to such subject easily as they get free run all across the host body without being intercepted by the natural immune system fully or partially. Comorbidities such as diabetes mellitus is proving fatal and life threatening as it was found out that in patients having diabetes mellitus and severe COVID-19 conditions, the administration of corticosteroids such as dexamethasone and methylprednisolone worsening the condition that the CFR for such patients is almost 60 to 80 percent and majority of the patients had to lose an eye in order to stop the spread of black fungus which is the implication of over administration of corticosteroids and TCZ(15).

PREVENTIVE MEASURES FOR COVID-19.....should be correlated with tocilizumab

Coronavirus disease 2019 or COVID-19 is a rapid evolving disease which has no available treatment considering its novelty. The drugs are being used to treat are repurposed drugs which has its own limitations. Therefore it is important to understand the importance of the preventive measures which can not only protects you from being infected but safeguards you from all the trauma that one had to face during infection and treatment of COVID-19. Wide ranges of preventive measures are well tested in previous such instances where the disease was contagious

in nature. The preventive measures which includes wearing proper mask properly, maintaining physical distancing in crowded places, not going places when not necessary as it can stop the spread, isolate one selves and report to nearest COVID-19 facility, vaccination are some of the major preventive measures. Wearing masks and maintain physical distancing have proven beneficial in the previous similar outbreaks of severe acute respiratory syndrome (SARS) and middle eastern respiratory syndrome (MERS) which were also caused by the viruses of the coronavirus families(16). As the virus is spreading among millions of people, its natural course is to mutate. Mutations are sometime sever which can evade the treatment and makes clinical management of the patient complicated. Therefor it is extremely necessary to acknowledge that wearing masks and maintain physical distancing are part and parcel of life especially in COVID-19 era. There is widespread reporting of the persistence of COVID-19 symptoms post recovery too. Many patients who got discharged from COVID-19 condition have been reporting recurring symptoms which are generally identified with COVID-19. This include impairment in taste and smell, headaches, reduced physical capacity with muscle aches, anxiety and depression and so on. These conditions are new and researchers are trying to grapple the hold over such scenarios. Hence it is extremely important to follow all COVID-19 appropriate behavior. Also various vaccine candidates are in fray and one needs to get their jab as soon as possible. Vaccine is yet another proven preventive measure which protects you from being severely ill due to COVID-19 infection(17). Although it does not guarantee protection from infection from COVID-19 but it does ensure that vaccinated person does not slip into grave medical condition which are severe in nature and difficult to handle clinically(18-20). It provides a holistic cover. Also one must wear mask and maintain physical distancing as one is always prone to the infection(21-22). Also certain mutations are found to be evading the cove of vaccine which is a great cause of concern. Although vaccines are till now proven an effective weapon against war against COVID-19.(23-32)

CONCLUSION

Coronavirus disease 2019 or COVID-19 is the unprecedented medical and social emergency which needs to be tackled with utmost priority. The repurposed are proving effective in certain cases but extrapolating can cause the disastrous pandemic to worsen further. Tocilizumab which is actually a drug administered in the patients of rheumatoid arthritis is proving beneficial among certain section of COVID-19 infected patients who are critically ill. But it has certain limitations too. Over reliance on one particular drug can create mayhem as was seen in over use of corticosteroids like dexamethasone which accelerated the case fatality rate. Therefore the decision of administration of a particular drugs must be vested with the chief medical officer of the COVID-19 facility. Bottoms up approach can prove beneficial and can result into effectively strategizing the fight against COVID-19. Preventive measures are the best way to deal with new disease outbreaks like COVID-19. **Vaccination so among the most effective way especially in comorbid patients as they are more vulnerable to slip into severe medical conditions. Millions of people are already vaccinated but millions more prone to infection and need to be vaccinated on war footing. Vaccine nationalism must be set aside and low and middle income countries where most of the population of the world resides, should be vaccinated as even one case can culminate into another disaster as was seen during highly contagious COVID-19.**

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