Review

Role of IL6 Antagonist, Tocilizumab in Treating Covid 19; A Narrative Review

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Abstract

Background and objective: Coronavirus disease 2019 (Covid 19) is the most severe pandemic hit the world during the last century. Generally, the diseases course has two phases, a viral phases and a more damaging immune mediated phases. The latter might lead to major organ failure and even death. Many therapeutic options have been tried most of them was not proven regarding safety and efficacy. Tocilizumab is the most widely used cytokine antagonist in order to combat for the cytokine storm of covid 19. It is an Anti- IL 6 monoclonal antibody used in severe cases to reverse the expected cytokine storm. Until recently, there is insufficient data regarding indications, safety, efficacy and exact dosing regimen of tocilizumab. The current narrative review tried to answer the above parameters in question.

Method: This is a narrative review involving the effectiveness, the dose and indications of tocilizumab as a treatment option for covid 19 infection. To do so, search on Pubmed using the following keywords: tocilizumab, covid 19, effectiveness, dose and indication with varying mixes.

Results: the search results revealed a total of 514 results, of them only 236 were included in this review.

Conclusion: Tocilizumab, is highly effective therapy especially for severe and critical covid 19 infections. The usual recommended dose by FDA (up to 3 infusions of 8 mg/ kg body wt.) is the rule, but can be used in a lower dosage and as a single dose, also.

Keywords: narrative review, tocilizumab, covid 19, effectiveness, dose and indication.

Introduction

By August, 17th 2020, World Health Organization has recorded 21,549,706 confirmed covid19 infections and about 767,158 deaths due to this pandemic all over the world [(1)]. One of the leading cause of mortality is the cytokine storm lead by IL6. A group of therapeutic agents targeting this cytokine were introduced. The single most important agents of them is tocilizumab, an anti IL6 receptor antibody already used to treat rheumatoid arthritis [(2)] and cytokine Release Syndrome [(3)]. Moreover, It is used in critical and severe cases to combat cytokine storm of covid 19 infection [(4,5)]. Yet, full knowledge regarding effectiveness, dosing and indication is uncertain about this drug when used to treat such a condition [(6)]. The current review tried to unmask some of this uncertainty.

Method

The current narrative review implements PubMed as the scientific search engine to answer some queries about targeting IL6 by using tocilizumab therapy and its role in Covid 19. The targeted studies were randomized clinical trials, systematic review, case report, observational analyses and prospective cohorts. Using the Keywords tocilizumab and covid 19 (search1) we got 346 results on PubMed. Searching the same engine with the Keywords; tocilizumab effectiveness and covid 19 (search2) the number of results

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were 127 results. While by entering the Keywords tocilizumab, indications and covid 19 (search3), there were 11 results. By using the Keywords tocilizumab, dose and covid 19 (search4), we collect 30 results. Some of the obtained results were omitted due to repetition and irrelevance. Only 236 results from all search processes were harvested and included in this narrative review.

Therapeutic effectiveness of tocilizumab in Covid 19

Almost all of the truly harvested studies reveal that tocilizumab is effective in treating Covid 19. This was measured via clinical, radiological and biochemical parameters after tocilizumab therapy.

Tocilizumab performs its therapeutic effect via binding to IL-6 receptors, thereby blocking wide variety of immune cell signaling and thus combatting cytokine storm /release syndrome [(7)].

Studies have shown that tocilizumab relieves fever and tachycardia associated with cytokine release syndrome (CRS) within hours [(8,9)]; while there is some delay in resolution of hypotension and organ malfunction (10). Furthermore, it was reported that a longer delay of using tocilizumab leads to an increase in CRS-related cardiovascular complications [(11)]. Owing to the above data tocilizumab represented a backbone drug to combat life threatening complications of CRS [(12,13,14)]

A Study conducted in China, during April 2020 enrolled 21 severe and critically ill patients who administered tocilizumab, 20 of them obtained full recovery and the last one was still in the ICU at time of publushing the paper. [(15)]. Thereafter, more promising results were expected from wider clinical trials performed latter on, enrolling about 500 patients [(16)]

In an Italian clinical trial, tocilizumab results in a reduction of O2 requirement, improvment of CT lung opacity, normalization of lymphocyte count, decrease of C-reactive protein and hospital discharge, with hospitalization period of about 13.5 days.[(17)]

A Chinese prospective clinical trial, involved 21 patients with ARDS and CRS whom given tocilizumab. The result was a dramatic decrease in IL-6 levels and body temperature, with improvement in lung function. In addition, 90% of patients got a decrease in the ground glass opacity on lung CT, and normal lymphocytes population. [(18)]

Tocilizumab was given to 20 patients with severe or critical conditions in addition to routine treatment. Few days later, the fever and all other symptoms were off. Oxygen intake was reduced in 15 patients and help one patient to quit oxygen therapy. Pulmonary CT scans improvement in 19 patients. On day 5 of tocilizumab, the lymphocytes count and CRP got normalized in 10 and 16 patients, respectively. Interestingly, 19 patients were discharged after 13 days of tocilizumab treatment. [(17)]

Likewise, in a single-arm prospective trial on off-label use of tocilizumab for 63 hospitalized patients with severe COVID-19 infection. The results were promising with marked improvement in the levels of ferritin, C-reactive protein, D-dimer and (Pa02) to (Fi02) ratio. The mortality rate was reduced down to 11% [(19)]**.** Furthermore, other trial stated that tocilizumab reduces the need for ICU admission and/or decreases mortality rate. [(20)]

In an Italian prospective clinical trial, tocilizumab given (as single dose) to 62 out of 85 patients with severe COVID-19 Pneumonia. The results were significantly increased survival rate, decreased mortality rate and dramatic improvement of pulmonary functions.[(21)]

Indications of tocilizumab in Covid 19

According to FDA, tocilizumab is recommended for adults and pediatric patients aged ≥ 2 years with severe or life-threatening CRS to be used alone or in combination with glucocorticoids.[(22)]

On March 3rd, 2020, the Chinese National Health Commission issued the "New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Seventh Edition)".

Whereby, the indications of tocilizumab in Covid 19 are "patients with extensive lung disease and severely ill patients, and those with elevated IL-6 levels detected by the laboratory" excluding patients with active infection like TB [23].

However, many clinical trials adopted somewhat different conditions for using tocilizumab. Example, Xiaoling Xu *et al.* used tocilizumab in patients with COVID-19 in the presence of one of the following criteria: i) respiratory rate ≥ 30 acts/min; ii) SpO2 ≤ 93% in ambient air; iii) PaO2/FiO2 ≤ 300 mmHg.[18].

Although tocilizumab was principally used in an attempt to reduce lung damage in patients with severe SARS-CoV-2 infection [17,19,21,24-28], and because tocilizumab is capable of inhibiting the overactive inflammatory process, thus it can be used also in early mild and moderate stages of COVID-19 infection.[28]

Tocilizumab has been used for critically ill patients on mechanical ventilator. In a cohort study involved 154 mechanically ventilated COVID-19 patients, tocilizumab had reduced the mortality rate, despite increased risk of superinfection.[29] However, a previous study (SMACORE) revealed that tocilizumab administration did not reduce ICU admission or mortality rate in a cohort of 21 patients. [30]. Aproximately similar results were obtained by another retrospective cohort of 35 patients with severe COVID-19 Pneumonia.[31]

Serum level of IL6 represented an important indication marker for tocilizumab therapy. In addition, its elevated levels early after tocilizumab can predict who will benefit from tocilizumab and pass the CRS. Thus, post tocilizumab IL6 level may indicate the need for more potent targeting of IL-6.[32]

In a case report, a patient who was liver transplant recipient on hemodialysis, presented with COVID-19 pneumonia, and developed marked inflammatory manifestations with rapid improvement after administration of off-label, single-dose tocilizumab.[33]

Dose regimen of tocilizumab in Covid 19

It is recommended, by FDA, to give tocilizumab by IV infusion in a dose of 8 or 12 mg per kg body wt for patients weighing more or less than 30 kg, respectively in case of cytokine release syndrome. It is received by slow-drip infusion over one hour. However, it is not recommended to exceed 800 mg per single infusion. Doses can be repeated once or twice with 8 hours apart, with max. 3 doses, as indicated. [22]

On the other hand, the Chinese Clinical Guidance for Covid 19 pneumonia Diagnosis and Treatment recommended this regimen of tocilizumab for extensive lung damage and severe disease as follows; for the first dose of 4–8 mg/kg, the recommended dose is 400 mg, diluted to 100 mL with 0.9% sodium chloride, and the infusion time is more than 1 h. For patients with poor efficacy of the first dose, an additional dose (the dose is the same as before) can be applied after 12 h, with a maximum of 2 cumulative doses and a maximum of 800 mg for a single dose [4].

A Chinese pilot study used tocilizumab for patients with severe COVID-19 infection at a dosage of 400 mg intravenously in a single dose, such a dose might be repeated in case of no improvement [18].

Another ongoing clinical trial (CONVACTA) involved two sets of hospitalized severely affected patients group (in addition to placebo); the first set will receive 1 intravenous infusion of tocilizumab , dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose may be given if clinical symptoms worsen or show no improvement. The second set would administer one 400 mg dose of IV tocilizumab and additional dose may be given if clinical symptoms worsen or showed no improvement [34].

Likewise, another clinical trial involved 27 patients (most were intubated) given single 400 mg intravenous dose of tocilizumab with excellent clinical, radiological and biochemical improvement [25].

A case report of critically ill intubated patient with ARDS unresponsive to any therapy revealed dramatic improvement after single 800 mg intravenous dose of tocilizumab [26].

In SMACORE retrospective cohort, tocilizumab was administered to 21 patients. The first infusion was 8 mg/kg (up to a maximum 800 mg per dose), repeated after 12 h if no side effects were reported after the first dose [30].

However, single tocilizumab infusion was shown to give very promising clinical outcomes in the Italian prospective cohort [21]. These findings go with those of another retrospective clinical study which administer low dose subcutaneous tocilizumab 162 mg at least once to 12 patients with proven severe covid 19 pneumonia and CRS [35].

Although small sample size, another study has shown that low-dose subcutaneous tocilizumab (324 mg) may be a safe and promising add on therapeutic option in 10 patients with moderate COVID-19 (who administered tocilizumab) compared to 10 other patients with routine treatment only [36].

Conclusion

Tocilizumab is relatively effective therapy especially in severe and critically ill covid 19 patients. However, some other studies suggest using tocilizumab at any phases during the infection course**.**

The recommended dosing regimen is as stated by FDA (three doses of 8 mg /kg body wt., maximum 800mg/ dose via intravenous infusion, at least 8 hours apart). Varying modification of such a dose was observed. Single infusion and lower dosing are examples.

Recommendation

It is recommended to use tocilizumab to treat severe and critical covid19 infections alone or as an add-on therapy according the recommended dosage regimen adopted by FDA. Minor dosage modifications are followed by varying clinical trials.

Conflict of interest

The author declares no conflict of interest.

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