

Review Article

ENCOURAGING EFFECT OF TOCILIZUMAB AND REMDESIVIR IN TREATMENT OF COVID-19Barrawaz Aateka Yahya*¹, Shahajan Shabbir Baig²

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ABSTRACT

Novel corona 2019 further named, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the outbreak has started from Wuhan city of china in December 2019 and within short span, its spread in almost 200 countries, and hence world health organization declared it a pandemic emergency. At present no licensed therapy presents or vaccine or effective agents available in the management of COVID-19. The severity of this virus can be categorized into three phases initial mild symptomatic phase, respiratory infection phase, and Cytokine storm phase. The initial mild symptomatic phase can be identified by a cough, fever, severe diarrhea, tastelessness, etc. In some clinical trials, these symptoms are treated with traditional therapy such as azithromycin, lopinavir, etc. But if not treated, it leads to pneumonia, responsible for the shortening of breathing but apart from this currently available data has shown a correlation between proinflammatory factors like interleukin and COVID 19 infections. Tocilizumab, USFDA approved in the treatment of Chimeric antigen receptors T cell therapy and now shown effectiveness in COVID-19 especially against cytokine release syndrome and lowered the mortality rate, however outcome of ongoing clinical trials will prove its confirmatory treatment against COVID-19. For such severe pandemic disease, other promising agents like Remdesivir or Tocilizumab that's giving a really high recovery rate with reduced mortality rates in severe condition of COVID-19. Because of the severity and mortality rate from COVID-19, the globe needs promising, efficient treatment, sharing early discharge of patients, and reduced mortality which can be expected from Tocilizumab or Remdesivir in near future.

INTRODUCTION

An outbreak of incomprehensible pneumonic cases have been found in Wuhan city of China in December 2019, this zoonotic disease further named coronavirus disease (COVID 19) and further proliferated globally since then and as of now, almost infected over 21.9 million peoples worldwide and the global number of deaths are 774379 patients now ^[1]. The majority of the peoples has suffered from symptomatic which shown symptoms like dry cough, fever, severe diarrhea, tastelessness or temporary loss of smell sensation, physical weakness, body pain, or have asymptomatic symptoms. Regrettably, these mild

symptoms further leading to severe pneumonitis, severe shortness of breath, and effect on other major organs like the heart and kidney ^[2]. But pneumonia caused by this COVID-19 is different from, pneumonia brought by other respiratory viruses in terms of mildness and duration of the inflammatory response which is generally run by the innate immunity, some pro-inflammatory cytokines ^[3].

Moore et al explained the mechanism of severing SARS COV-2 and the relationship between Cytokine and especially interleukin -6 (IL -6) and an inflammatory

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response given by the body immune system through the Cytokine cascade cycle which further can be antagonized by some immunosuppressive agents^[4]. Cytokines like interleukin 6 (IL-6) are one of the most important agents responsible for inflammatory reaction and immune response, beyond this most of the COVID-19 infected patients have been noticed with the elevated level of IL-6 which are further resulted in death^[5]. Even pathogenesis of severe acute respiratory syndrome (SARS) has been revealed that Cytokine storm has been the main factor which further involving the distinguished release of pro-inflammatory factors like TNF- α , Interleukin 12 (IL-12), IL-6^[6], and same clinical characteristic related with Cytokine storm in COVID-19 has been analyzed and explained in recently published multiple research papers published^[7,8,9].

Apart from above mentioned pro-inflammatory elements, there are some other major factors also found in the report of ICU hospitalized severe COVID-19 patients (Ultimately responsible for death), like monocyte chemo attractant protein (MCP-1), interleukin-7 (IL-7), interleukin-10 (IL-10), interferon- γ (IFN- γ) inducible protein, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein 1 α (MIP 1 α) were found in ICU patients, which implied that a cytokine storm occurred^[10,11]. Because of this pandemic situation, recently Bourboulis G et al, has studied the immune responses of 54 patients and found an abnormal or variant immune pattern such as increased Cytokine production and increased circulating cytokines especially IL-6 and in other cases, it is defective in the lymphoid system function associated with interleukin mediated decreased in human leukocyte antigen D related (HLA-DR expression) in patients with COVID-19^[12]. After analyzing current pathogenesis especially following pro-inflammatory factors, interleukin inhibitory therapy may be of benefit in severe COVID-19 infection^[13].

Because of such a variable and abnormal global pandemic emergency associate with the variable effect of COVID-19, there should strategy mitigation of treatment that can concomitantly manage the antiviral activity along with immuno modulatory effect and adjunctive effects. Up till now, there is no licensed or

approved treatment for COVID-19 established by a regulatory authority, but since because of the clinical severity of COVID 19 connected with Cytokine release and overproduction of soluble inflammatory mediators, several agents who can modulate immune response are under investigation and clinical trials.

Tocilizumab

This pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has turned global concern because of its infectious nature which resulted in the hospitalization of the majority of patients in ICU (intensive care unit), ultimately resulted in deaths. Because of induced inflammatory factors which further leading shortness of breathing and ultimately leading to acute respiratory distress syndrome (ARDS). So in the absence of approved treatment, the main challenge is to prevent these inflammatory stimuli and to overcome symptoms like dyspnea, dry cough, mild or symptomatic high fever^[14].

Tocilizumab is a biologic product especially having peculiarity of monoclonal antibody and working through blockage of interleukin - 6 receptor^[15], the main reason behind using this drug in rheumatoid arthritis and sometimes with conventional disease-modifying anti-rheumatic drugs (DMARDs)^[16]. Because of the cytokine storm notion, the main target must be to reduce elevated serum levels of pro-inflammatory cytokines. Cytokine is also observed in some inflammatory diseases like Primary Sjögren's syndrome, systemic lupus erythematosus, non-infectious uveitis, and Rheumatoid arthritis. A systemic study with several research papers indicated that Tocilizumab is effective in Takayasu arthritis (although in limited terms), a rare inflammatory disease^[17]. So severe pneumonitis patients with COVID-19 might be treated easily by this therapy^[15]. The antagonistic mechanism of Tocilizumab tried to explain with the help of published literature and with some clinical trial studies^[16], but confirmation needed large scale clinical trial studies that will answer some unsolved questions about the exact mechanism through which this Cytokine inhibition occurs. In August 2017, USFDA has approved Tocilizumab the treatment of patients 2 years of age or older with cytokine release syndrome (CRS) that occurs with chimeric antigen

receptor T cell therapy (CAR T-cell therapy) [17,18]. Like CAR- T therapy, Tocilizumab treatment can be made in Cytokine release syndrome in patients having COVID-19 [19].

Efficacy of Tocilizumab to reduce mortality rate was analyzed in 21 severe patients of COVID-19, with the simultaneous medication of including lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy. This resulted in improved overall symptoms and respiratory function and which indeed defined the antagonistic nature of Tocilizumab against IL-6 [20]. Another multi-centre observational study has revealed that hospitalized ICU patients suffered from severe SARS-CoV-2 has reduced mortality rate when Tocilizumab exposed [21]. Enthusiastically, efficacy of Tocilizumab via the intravenous or subcutaneous route of administration has been evaluated in a cohort study (supplemental oxygen, Hydroxychloroquine, azithromycin, antiretroviral, and low molecular weight heparin). Although alone therapy of Tocilizumab is effective against severe COVID-19 patients, in combination with glucocorticoids (like methylprednisolone) it can be useful for lowering fever, CPR, and the body's white blood cells which are further assistant for anti-inflammatory therapy [22].

When patients with severe COVID-19 were treated with Tocilizumab, a retrospective cohort study resulted in a shorter median time for clinical improvement along with a non-significant shorter duration of invasive ventilation (Concomitant systemic dose of azithromycin, Hydroxychloroquine, and systemic steroid was given). Although this study was clinically important, certain limitations proved further confirmation via clinical trials, as concomitant medication might be affected on final results, short duration of the study, and short sample size [23]. An observational study among 2512 US based patients has shown enthusiastic analysis for treatment with Tocilizumab which encourages the deep study of the same, however, comparative parallel treatment given i.e. Hydroxychloroquine did not satisfied about the reduced mortality rate among hospitalized severe patients of COVID-19 [24]. A retrospective cohort study of 1351 patients has been done (included 40% of patients suffered from severe pneumonia) given intravenous and

subcutaneous Tocilizumab and assumed about lowering death rate risk in patients with severe COVID-19 pneumonia. However, this study had left behind certain limitations concerning study design, drug dose, different gender response, some patients enrolled having a disease like cancer, hope these limitations will be addressed future clinical trial studies [25].

Pietro S et al analyzed the case study with the help of computed tomography analysis in 50 years old age patient history of Follicular non-Hodgkin lymphoma previously treated with chemotherapy and after analyzing reports of COVID-19, suggested that, Tocilizumab can block the downstream signal transduction by binding mIL-6R and sIL-6R, and it plays a role in the treatment of cytokine storm caused by COVID-19 [26]. Various phases of the severity of infections may be deciding the therapy to be given in COVID-19 patients, phases like pulmonary, inflammatory, or mild infections, can be treated with diverse agents but among which Tocilizumab and Remdesivir have shown clinical improvement of patients and anti-inflammatory effects with the help of published studies [27].

Despite of all positive clinical outcomes and contribution in COVID-19 pandemic disease of Tocilizumab, limitations or hidden risks like patients of systemic sclerosis and lymphoid dysfunction with interleukin-6 mediated decrease in HLA-DR expressions need to be addressed [28,29].

Remdesivir

Among the currently available data or studies, the relevant antiviral effect of Remdesivir against the current pandemic medical emergency of COVID-19, are those that have been genetically somewhat near to coronavirus [30]. Remdesivir is a broad-spectrum antiviral drug that has shown action against RNA viruses in several families, including Corona viridae (such as SARS-CoV, MERS-CoV, and zoonotic coronavirus strain capable of infecting human respiratory epithelial cells) [31]. The US Army Medical Research Institute of Infectious Diseases (USAMRIID) and Centers for Disease Control and Prevention- (CDC) Collaborated to discover antiviral agent against RNA viruses with the potential to induce a

global pandemic (e.g. Ebola virus, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) Coronaviruses) [32-33].

But the viral mechanism has been elaborated in a controlled randomized study in Ebola virus, Remdesivir (which is a prodrug) has given in one arm of the trial, further metabolized into active form GS -441524, responsible for promoting evasion of proofreading by viral exo-ribonuclease leading to viral RNA synthesis inhibition. Through this mechanism, viral load and infection decreased which ultimately dose-dependent effect [34]. In another study, conducted by Wang and his teammates, a randomized, double-blind, placebo-controlled, multi centre trial with an IV dose of Remdesivir with different dosage regimen and were well tolerated by the patients. Although prominent effects did not reveal in severe cases of COVID-19 patients from this study but Remdesivir has improved recovery time with a reduced mortality rate as compared to placebo which suggests some improved clinical outcomes with this [36-38].

Regardless of not having sure and confirm results or licensed value, the Benefit-Risk Action Team (BRAT) framework was used to evaluate risk assessment for Remdesivir in the clinical trial and shown favorable effects by shortening the time of recovery in patients treated with Remdesivir along with non-significant reduced mortality risk [34].

Rare but some in vitro studies have further pushed up the in vivo support like Hashemian et al has analyzed various in vitro and in vivo studies and demonstrated about the improved clinical efficacy of severing corona patients upon treatment by Remdesivir [35]. Not only in vivo but also in vitro study of Remdesivir in combination with chloroquine has shown positive results against COVID-19 and suggested to have a reflection of efficacy in severe patients of COVID-19 [39-43]. However, still, there are certain ambiguities with the positive role of Remdesivir in terms of clinician's validation towards their patients [44].

CONCLUSION

In the current pandemic situation, a promising, repurposing, or repositioning treatment execution for

COVID-19 in association with the therapy which compensates the prevention of critical illness is the immense challenge to global medical science. Although several studies, research works, and analytical research encouraging on already listed agents and potential benefits for COVID-19 but convinced results to remain indecisive. Most of the research work has elaborated about the mild to severe symptoms which further leading to hospitalization, sometimes due to pneumonia, overproduction of pro-inflammatory cytokines (Cytokine storm). These symptoms are being treated with Remdesivir or Tocilizumab for the stability of patients and to reduce viral loads, through anti-inflammatory mechanism or might be reducing mortality rate. But apart from these weighed benefits, still the research field is unanswered about the safety and risk issue of these agents which must be addressed concerning potential adverse events on large scale clinical investigation. Future perspective can be expected for confirmed therapy of Tocilizumab or Remdesivir.

Abbreviations used

BRAT: Benefit-Risk Action Team, **CAR T-cell:** Chimeric Antigen Receptor T Cell Therapy, **CDC:** Centers for Disease Control and Prevention **CRS:** Cytokine Release Syndrome **DMARDs:** Disease Modifying Anti-rheumatic Drugs **HLA-DR:** Human Leukocyte Antigen DR Iso type **G-CSF:** Granulocyte Colony Stimulating Factor **IFN- γ :** Interferon- γ **IL:** Interleukin **MCP 1:** Monocyte Chemo attractant Protein **MIP 1 α :** Macrophage Inflammatory Protein -1 α **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus- 2 **TNF- α :** Tumor Necrosis Factor- α **USAMRIID:** The US Army Medical Research Institute of Infectious Diseases **USFDA:** United State Food and Drug Administration

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