Use of tocilizumab for treatment of COVID-19 from off-label to extended indication

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INTRODUCTION

Insufficient scientific evidence and limited clinical experience in COVID-19 treatment, imposed the need for off-label use of existing drugs originally approved for other diseases and indications. As it has been demonstrated that interleukin-6 (IL-6) plays a pivotal role in the inflammatory response associated with COVID-19 infections, a large focus has been placed on IL-6 and IL-6 receptor inhibition. One such agent is tocilizumab, a monoclonal antibody that acts as a competitive IL-6 receptor inhibitor (Figure 1). Originally marketed as an anti-rheumatic drug, tocilizumab has gained significant importance during the pandemic, and is currently one of the few drugs officially recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of COVID-19.

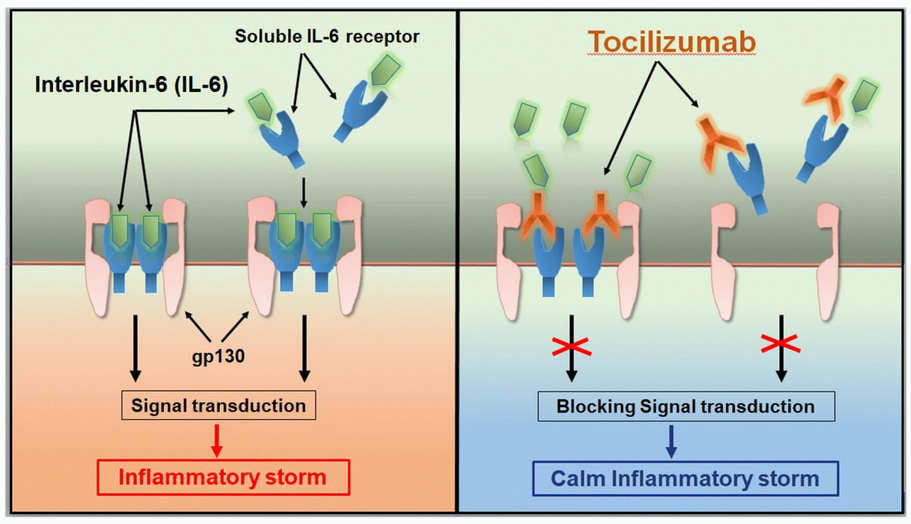

Figure 1.

OFF-LABEL USE OF TOCILIZUMAB IN COVID-19 TREATMENT

The most important scientific evidence on its potential benefit came from the RECOVERY and EMPACTA trials. The obtained data showed that tocilizumab improved survival and other clinical outcomes, and thus was superior in comparison to standard care alone (RECOVERY) and placebo (EMPACTA). Importantly, these benefits were most clearly seen among patients treated with systemic corticosteroids what letter on become standard of care for COVID-19 patients requiring treatment with oxygen.

Following initial positive results from large clinical trials, as well as the off-label use experience in global clinical centers, tocilizumab administration was initiated in hospitalized COVID-19 patients in Republic of North Macedonia. Based on the data obtained from the University Clinic of Infectious Diseases and Febrile Conditions in Skopje, off-label use of tocilizumab was initiated in March 2021 in COVID-19 hospitalized patients with severe clinical symptoms and absence of contraindications. All of these patients required supplemental oxygen and received non-invasive ventilation. Moreover, all patients received symptomatic therapy concomitant with antimicrobial and antithrombotic agents, as well as hydration supplements. Some of them were also treated with systemic corticosteroids and/or additional antiviral treatment with remdesivir.

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EXTENDED USE OF TOCILIZUMAB

In June 2021, the FDA issued an Emergency Use Authorization (EUA) for the drug Actemra (tocilizumab) for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (FDA, 2021). At the end of 2021, EMA's Committee for Medicinal Products for Human Use (CHMP) also recommended extending the indication of the same drug registered under the brand name RoActemra (tocilizumab) to include the treatment of adults with COVID-19 who are receiving treatment with corticosteroids and require supplemental oxygen or mechanical ventilation (EMA, 2021).

Subsequently to EMA's approval, in January 2022, the Macedonian Agency for Medicines and Medical Devices (MALMED) approved extension of the indication of Actemra for the treatment of adults with COVID-19. The official COVID-19 protocol published by the Ministry of Health, was updated in February 2022 to include tocilizumab for treatment of hospitalized patients with progressive severe or critical disease.

CONCLUSION

The global health crisis caused by COVID-19 was a stark reminder of the lack of antiviral agents on the market, and the need for effective medical treatment for patients with severe clinical symptoms continues to be one of the biggest challenges. In lack of highly effective and targeted treatment and widespread vaccine hesitancy, regulatory authorities must accelerate their decision process in order to find an effective medical therapy in the shortest time possible. Off-label use is an essential part of pharmacoepidemiological studies and life cycle of the drug as a possibility for expanding to other indication.

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