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Short communication

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

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Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly developed into a worldwide pandemic causing a significant health and economic burden. Given the diverse clinical presentation, course, and progression of COVID-19, as well as the limited medical supply, regulatory authorities have faced a significant challenge in establishing robust regulatory programs in order to reduce clinical dilemmas in selecting proper therapy for COVID-19 patients. Several regulatory approaches were used for accessing potential therapies in COVID-19 as clinical trials, compassionate use, emergency use and off-label use (Halimi et al., 2020).

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. Off-label drug use indicates the prescription of drugs other than that for which they have been officially approved, with respect to dosage, age, indication or route of administration. Decision for off-label use should be made on a case by case basis, weighing the risks and benefits of treatment for each patient.

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. 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.

Off-label use of tocilizumab in COVID-19 treatment

The beneficial effect of tocilizumab in COVID-19 management was initially recognized in a study conducted in Wuhan, which encouraged Italian clinicians to precede an off-label use of tocilizumab in treatment of patients with severe COVID-19 pneumonia. Tocilizumab immunotherapy strategy has been formally included for the first time in the treatment of patients with SARS CoV-2 infection, by the National Health Commission of China, in March, 2020, with the lists of key criteria: diagnosis and treatment of patients with severe or moderate clinical condition diagnosed with increased laboratory level of IL-6 (Panovska et al., 2021).

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

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corticosteroids what letter on become standard of care for COVID-19 patients requiring treatment with oxygen. (FDA, 2021; EMA, 2021).

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.

Extended use of tocilizumab

In June 2021, 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, 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 Ministry of Health, was updated in February 2022 to include tocilizumab for treatment of hospitalized patients with progressive severe or critical disease. According to the protocol, tocilizumab should be administered as intravenous infusion at a dose of 8 mg/kg, with maximum dosage of 800 mg per infusion. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of Actemra may be administered 12-24 after the initial infusion.

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. Assessing off-label of drugs is important way to highlight clinical indications in diseases where specific research needs to be conducted. This regulatory approach for accessing potential therapies is less time-consuming since the safety and pharmacological profile of particular drug has already been established.

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