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REVIEW ARTICLE

The use of tocilizumab in severe COVID-19: a comprehensive review

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Summary

This review focuses on the therapeutic application of Tocilizumab (TCZ) in the treatment of COVID-19, specifically exploring its mechanisms, safety aspects, clinical efficacy, dosing strategies, and outcomes in the Serbian context. TCZ, acting as an IL-6 receptor inhibitor, mitigates the cytokine storm observed in severe cases, leveraging its structure and pharmacokinetics. While the overall safety profile indicates good tolerability, there are subtle concerns regarding the occurrence of rare complications in critically ill patients. Clinical trials, with certain variations, emphasize the need for careful interpretation of indications and patient selection for TCZ therapy. Current protocols in place in the Republic of Serbia recommend the use of TCZ at a dose of 8 mg/kg body weight based on clinical parameters and inflammation markers, primarily IL-6 levels. Literature review suggests that during TCZ shortages, dosing may be adjusted to 400 mg as a single dose in the treatment of severe COVID-19. The optimal timing for initiating therapy coincides with the phase of increased inflammation (7-10 days after symptom onset), with an emphasis on patient selection based on biomarkers, disease severity, and the need for respiratory support. Combining TCZ with corticosteroids shows reduced mortality, necessitating cautious dosing. Potential benefits arise from combining TCZ with remdesivir, NSAIDs, and anticoagulants, requiring careful dosing and monitoring. Retrospective studies in Serbia report positive outcomes, highlighting the potential of TCZ in treating severe cases. In summary, TCZ shows promising results in the treatment of COVID-19, necessitating further research and careful patient monitoring, especially in resource-limited settings.

Key words: Tocilizumab, severe COVID-19, effectiveness, safety, experiences

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INTRODUCTION

The emergence of coronavirus disease 2019 (COVID-19) represents a global health crisis of unprecedented proportions (1). The World Health Organization (WHO) declared the COVID-19 pandemic on March 11, 2020, and the first case in Serbia was recorded on March 6, 2020 (2-4). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) attaches to angiotensin-converting enzyme 2 (ACE-2) receptors, triggering the activation of Th1 lymphocytes and the subsequent generation of proinflammatory cytokines, such as interleukin-6 (IL-6) and granulocyte colony-stimulating factor (GM-CSF) (5-7). Considering the significant role of IL-6 in cytokine release syndrome (CRS), it has been identified as a potential target for therapeutic interventions in severe patients (8).

Tocilizumab (TCZ) is a genetically engineered humanized monoclonal antibody specifically crafted to inhibit IL-6 receptors, thereby reducing its impact on the pathogenesis of COVID-19 (9-12). As per the guidelines set by the European Medicines Agency, TCZ was authorized for use in adults experiencing severe COVID-19 (13, 14). TCZ, as one of the utilized modalities of biological therapy started to be employed in Serbia (15, 16).

Prior to its therapeutic application in COVID-19, TCZ had been utilized in the treatment of connective tissue disorders such as rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis [17, 18]. Additionally, it has been employed for the treatment of cytokine release syndrome induced by T cells with chimeric antigen receptors in both adult and pediatric patients aged over 2 years (19). The utilization of TCZ is indicated in patients exhibiting severe COVID-19 pneumonia, characterized by heightened inflammatory markers: CRP and IL-6 (15, 16, 20). Furthermore, TCZ is deemed appropriate for individuals experiencing a rapidly progressing respiratory failure, extensive lung infiltration, and systemic inflammation (15, 16, 20).

STRATEGIC TARGETING: TCZ IN IL-6 SIGNALING

IL-6 functions as a multifaceted regulator in various biological processes associated with inflammation, metabolism, and tumorigenesis, operating in an autocrine, paracrine, and "hormone-like" manner (21). In COVID-19, a meta-analysis of 1302 cases revealed a threefold increase in IL-6 levels in severe compared to mild/moderate cases (22). Elevated IL-6 concentrations correlated with bilateral lung damage, fever, and increased mortality. The risk of severe COVID-19 and death escalated at IL-6 concentrations >55 pg/ml and >80 pg/ml, respectively (22).

Its unique signaling system involves IL-6 receptors (IL-6R) and downstream molecules. IL-6R comprises IL6-binding chain (IL6-Rα) and transmembrane protein gp130 (IL6-Rß), initiating the IL6-induced signaling cascade upon binding to IL-6.IL6-Rα is expressed in specific cell types, while gp130 is present ubiquitously (23-25). The signaling cascade involves the dimerization of IL-6 and IL-6R complex with gp130, activating Janus kinases 1 and 2, leading to phosphorylation of gp130 [23-25]. Soluble IL6-Rα in the bloodstream, formed by proteolytic cleavage and alternative splicing, facilitates IL-6 circulation, enabling "trans-signaling" where IL-6 and sIL-6Rα bind to gp130 in cells lacking mIL-6Rα [23-25]. The pathogenic effects of IL-6 are primarily determined by trans-signaling, while classical (cis) signaling contributes to acute-phase response, Th17 and Th22 cell production, and T regulatory cell suppression (23-25). "Trans-presentation" on dendritic cells further expands IL-6 signaling, influencing the differentiation of pathogenic Th17 cells (23-25). **(Figure 1)**

TCZ, a monoclonal antibody with the capacity to antagonize the IL-6 receptor **(Figure 2)**. TCZ exhibits a molecular structure comprising two heavy and two light chains, encompassing 12 intrachain and 4 interchain disulphide bonds, resulting in a global molecular weight of 149 kDa (26). The pharmacokinetics of TCZ are nonlinear, characterized by a relatively long half-life ranging from 5 to 12 days (26). Numerous randomized controlled trials demonstrate TCZ's significant and sustained improvement in structural joint damage, health-related quality of life, and reduction in C-reactive protein levels in rheumatoid arthritis patients, as well as improvement in the quality of life in individuals with specific hematological malignancies and immunological deficits (27-30). Additionally, TCZ serves as an adjuvant therapy for the uncontrolled inflammatory state associated with hemophagocytic lymphohistiocytosis in visceral leishmaniasis (31). These specific indications should be taken into consideration for TCZ, given the described atypical clinical courses of COVID-19 in patients from Serbia with severe hematological and immunological deficits (32-34).

After intravenous administration, TCZ undergoes biphasic elimination from circulation (35). The total clearance of TCZ is concentration-dependent and represents the sum of linear and nonlinear clearance (35). Linear clearance, measured as a parameter in population pharmacokinetic analysis, was 9.5 mL/h. Nonlinear clearance, dependent on concentration, plays a crucial role at low TCZ concentrations (36). When the nonlinear clearance pathway saturates, at higher TCZ concentrations, further clearance is predominantly determined by linear clearance (36). The elimination half-life (t1/2) of TCZ is concentration-dependent. In a steady state after an 8 mg/kg dose every 4 weeks, the effective t1/2 decreases with decreasing concentrations in the dosing interval, ranging from 18 days to 6 days (36).

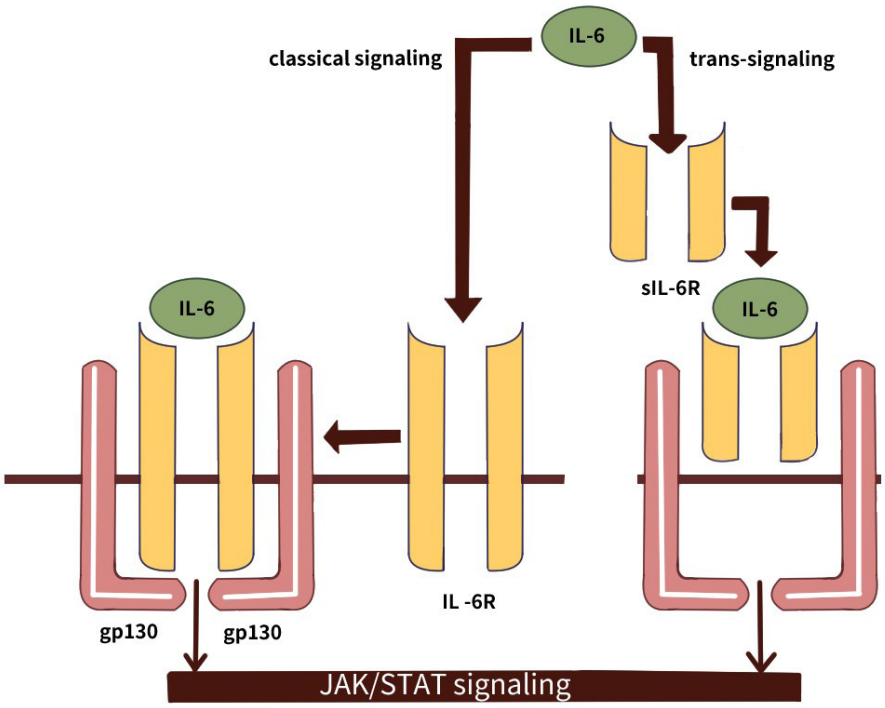

Figure 1. The image illustrates the IL-6 signaling pathway. IL-6 is transmitted either through the cell surface IL-6R or in the form of soluble IL-6R. This is followed by the dimerization of the signal transducer gp-130, which binds to the IL-6/IL-6R complex. Subsequently, activation of the JAK/STAT kinase pathway occurs.

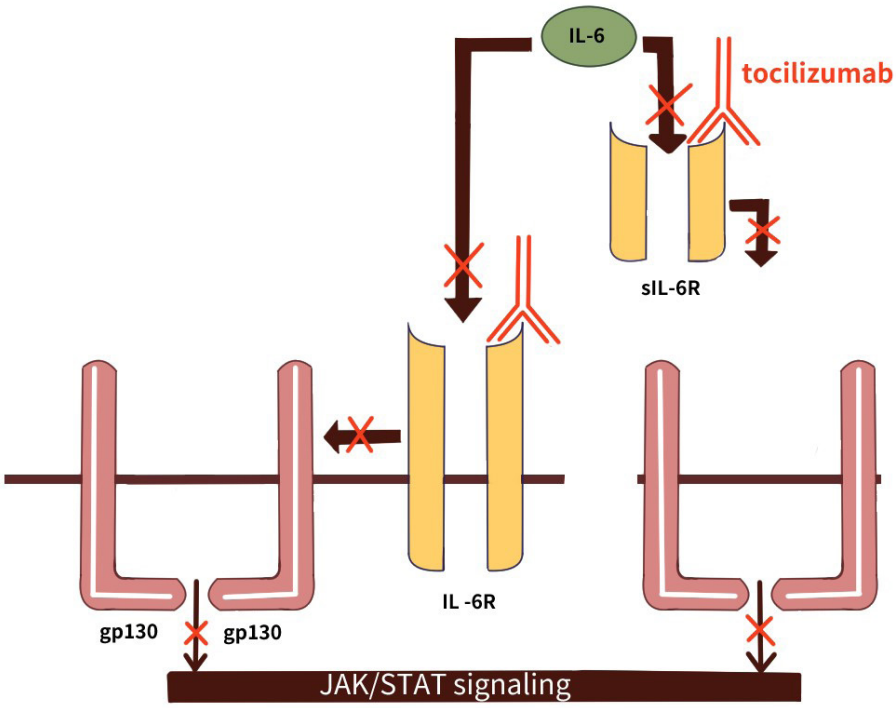

Figure 2. IL-6 classic and trans-signaling pathways, with a model of tocilizumab-mediated therapeutic receptor antagonism. Tocilizumab inhibits the binding of IL-6 to IL-6R or sIL-6R.

SAFETY PROFILE IN COVID-19 TREATMENT

Relevant literature data specific to the adverse effects of TCZ treatment in patients with COVID-19 have been analyzed. In terms of safety, our review suggests that TCZ is generally well-tolerated with a comparable rate of secondary infections in COVID-19 patients. The analysis of available literature did not reveal a significantly increased risk of secondary infections among individuals treated with TCZ (37-41). It's crucial to note that TCZ administration often involves patients with severe COVID-19, many of whom are in the intensive care

unit (ICU) or require ICU admission during follow-up (37,39). The anticipated higher incidence of infections in this subgroup can be attributed to various factors, notably the increased number of invasive procedures, including mechanical ventilation (MV), in severely ill patients (39).

In six-month controlled studies, the overall infection rate with TCZ 8 mg/kg plus disease-modifying antirheumatic drugs (DMARD) therapy was 127 events per 100 patient-years, compared to 112 events per 100 patient-years in the placebo plus DMARD group (42, 43). In the long-term exposure of patients, the overall infection rate in the TCZ group was 108 events per 100 patient-years (42, 43). In six-month controlled clinical trials, the rate of severe infections with TCZ 8 mg/kg plus DMARD therapy was 5.3 events per 100 patient-years, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group (42, 43). In monotherapy trials, the rate of severe infections was 3.6 events per 100 patient-years in the TCZ group and 1.5 events per 100 patient-years in the MTX group (42, 43).

In the long-term exposure population, the overall rate of severe infections (bacterial, viral, and fungal) was 4.7 events per 100 patient-years. Recorded severe infections (some fatal) included active tuberculosis, invasive pulmonary infections (such as candidiasis, aspergillosis, Pneumocystis jirovecii pneumonia), cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis (42). Cases of opportunistic infections were also documented (43).

Two cases of critically ill COVID-19 patients developing hypertriglyceridemia following TCZ administration have been reported (44, 45). This suggests that TCZ may induce a metabolic response in critically ill patients (44). IL-6, acting as an immunomodulator, has direct effects on metabolism, triggering the release of free fatty acids (FFA) from adipocytes and promoting glucose and FFA uptake by skeletal muscles (44). Another concern is the risk of intestinal perforation associated with TCZ use in critical COVID-19 patients, particularly those with preceding diverticulitis (45). The high expression of ACE 2 in the intestines, a key player in SARS-CoV-2 infection, provides a suitable medium for viral replication, leading to gastrointestinal symptoms such as abdominal pain (45). Changes in hemodynamics, induced by TCZ weakening the acute phase response, may cause low blood flow to the intestines, potentially resulting in intestinal perforation (45). This adverse effect may present without a significant escalation of CRP levels and might be overlooked in sedated and ventilated patients. In light of these findings, TCZ administration to critically ill COVID-19 patients has shown significant potential adverse events (45). Close monitoring of critical parameters, evaluation of therapeutic outcomes, and vigilance towards possible adverse effects influenced by concomitant drug activities are essential when employing TCZ therapy (44, 45).

TCZ administration in pregnant women with COVID-19 has demonstrated an absence of adverse effects on both the mothers and their newborns (46, 47). While a minimal risk of secondary infections was noted, it is advisable to maintain vigilant monitoring for infections, particularly when employing other immunosuppressive agents (47).

Interactions were only studied in adults. Simultaneous administration of a 10 mg/kg dose of TCZ with 10-25 mg MTX weekly has no clinically significant effect on MTX exposure (48). Population pharmacokinetic analyses found no impact of MTX, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids on TCZ clearance. Cytokines like IL-6, which stimulate chronic inflammation, suppress the expression of hepatic CYP450 enzymes (49). Hence, cytokine-inhibiting therapies like TCZ may enhance CYP450 expression. In vitro studies on human hepatocytes showed IL-6 decreases the expression of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzymes. TCZ normalizes their expression (50).

In an RA patient study, simvastatin levels (CYP3A4) dropped by 57% a week after a TCZ dose, reaching levels similar to or slightly higher than in healthy subjects (26). Initiating or discontinuing TCZ therapy requires careful monitoring for patients taking individually dosed drugs metabolized via CYP450 3A4, 1A2, or 2C9 (e.g., methylprednisolone, dexamethasone, atorvastatin). Doses may need adjustment to maintain therapeutic effects (42). Due to its long elimination half-life (t1/2), TCZ's impact on CYP450 enzyme activity can persist for several weeks after therapy cessation (47).

TCZ EFFECTIVENESS IN COVID-19

In the COVACTA trial, a multicenter Randomized Controlled Trial (RCT) involving 438 hospitalized patients, the impact of a single 8 mg/kg dose of TCZ was assessed (51). Notably, 36% of the TCZ group received concurrent dexamethasone, in contrast to 55% in the control group (50). Day 28 mortality and clinical status did not exhibit significant differences, but potential benefits in time to discharge and ICU stay duration were noted (51). Limitations of this trial include the absence of patient stratification for hyperinflammation signs and unequal corticosteroid use between groups (51).

The CORIMUNO-TOCI-1 trial, encompassing 131 patients with moderate or severe pneumonia, revealed no significant difference in day 28 mortality (52). However, there were indications of potential benefits, including a suggested reduction in ventilation or death by day 14, and no discernible increase in adverse events (52). Unequal steroid administration and a relatively small sample size may influence the perceived benefits of TCZ in this context (52).

In the EMPACTA trial, 389 hypoxemic patients received either one or two doses of TCZ (53). A statistically

significant reduction in progression to mechanical ventilation or death by day 28 was observed. However, overall clinical failure did not demonstrate a significant difference (53). The study's strengths include equal steroid use, adequate statistical power, and a focus on high-risk populations (53). Nevertheless, limitations are evident, particularly concerning the definition of the composite outcome.

Contrastingly, the RECOVERY trial, with its substantial cohort of 4116 patients, reported a 28-days mortality benefit associated with TCZ, especially when combined with systemic corticosteroids (54). TCZ recipients were more likely to be discharged alive, less likely to reach the composite endpoint, and exhibited a reduction in the use of hemodialysis or hemofiltration (54). The trial's robustness lies in its large sample size, diverse patient criteria, and the consistency of benefits observed across subgroups (54).

There is a lack of clear data on the impact of TCZ on the quality of life in COVID-19 convalescents. TCZ of exacerbations in rheumatoid diseases might provide a rough parallel.Patients treated with TCZ reported improvements in all patient-assessed outcomes, including the Health Assessment Questionnaire Disability Index (HAQ-DI) and the Short Form-36 questionnaire for functional assessment of chronic disease therapy (55). Statistically significant improvement in HAQ-DI scores was observed in patients receiving TCZ compared to those treated with DMARD (55). During the open-label period of Study II, improvement in physical function was sustained over 2 years. After 52 weeks, the mean change in HAQ-DI index was -0.58 in the TCZ group at a dose of 8 mg/kg (55, 56).

These trials collectively contribute to a nuanced understanding of TCZ's efficacy in COVID-19 treatment, emphasizing the importance of considering patient characteristics, treatment combinations, and outcome definitions in the interpretation of results.

TCZ DOSAGE STRATEGIES

The current treatment protocol for COVID-19 patients in Serbia, in accordance with the recommendations of the World Health Organization, involves the administration of TCZ when the IL-6 value exceeds 40 pg/ml, or when a threefold increase in inflammatory markers occurs within a one-day interval or the development of respiratory insufficiency (16, 20). The anticipated duration of TCZ therapy for COVID-19 treatment is one day, with a 12-hour interval between two daily doses (13, 16, 20). The recommended therapeutic dose of TCZ is 8 mg/kg of body weight, with a maximum individual dose of 800 mg (13, 16, 20).

The significant surge in COVID-19 cases has resulted in a shortage of TCZ, prompting healthcare practitioners to explore alternative options. Study findings indicate a comparable mortality benefit, although the 8 mg/kg dosing strategy may pose an elevated risk of fungal and viral infections (57). However, this investigation suggests a practical solution—employing the 400 mg dose—which could potentially lead to substantial cost savings, up to 50% (57). This cost-effective alternative not only addresses financial considerations but also preserves critical resources, enabling the broader administration of the medication to a greater number of patients (57). In the context of limited resources, such a strategy becomes crucial for optimizing healthcare delivery and ensuring the widespread availability of essential treatments during these challenging times.

TCZ TREATMENT TIMING

The consideration of optimal timing for initiating IL-6 blocking treatment requires a closer examination of specific days during the course of COVID-19. Existing studies have predominantly focused on patients in the advanced stages of the disease. To enhance precision in therapeutic decisions, it is suggested to postpone the administration of TCZ until the onset of the inflammatory phase, typically observed around days 7 to 10 after the initial symptoms manifest (58-61).

This proposed delay is grounded in the hypothesis that allowing the natural release of IL-6 during the acute infection stage may exert positive effects by hindering the proliferation of SARS-CoV-2 (60). The intricate dynamics of the immune response in COVID-19 further emphasize the importance of selecting an opportune time for intervention (61). Notably, amid the ongoing discourse among researchers, a consensus emerges on the potential efficacy of targeted immune suppressants like TCZ (58-61). The suggested window for initiating such therapies aligns with the period when patients begin to exhibit a noticeable trend towards hypoxia and inflammation, typically occurring around days 7 to 14 post-symptom onset (58-61).

OPTIMIZING PATIENT SELECTION FOR TCZ

Selection of patients for TCZ therapy in the context of COVID-19 involves a meticulous analysis of various biomarkers and clinical parameters. Studies like COVACTA and RECOVERY have provided deeper insights into these aspects (51, 54). In the COVACTA study, the analysis of biomarker values such as CRP, IL-6, and ferritin played a crucial role in identifying patient subsets most likely to benefit from TCZ (51). For instance, post hoc analysis revealed that high ferritin levels were predictive of a positive response to TCZ (62). Although there were no clinically significant differences in time to death by day 60 among subgroups based on CRP, IL-6, or ferritin

values, these biomarkers continued to play a pivotal role in identifying patients with a hyperinflammatory response (62).

In the REMAP-CAP study, which included critically ill patients, TCZ demonstrated efficacy in reducing the need for ongoing organ support and improving survival compared to standard therapy (63). This study further emphasized the importance of considering disease severity and the need for intensive support when selecting patients (63). RECOVERY, a large randomized trial, provided robust support for the use of TCZ in hospitalized COVID-19 patients. TCZ significantly reduced the risk of death by day 28 compared to standard therapy, regardless of the type of respiratory support (54). This study underscored the importance of interpreting results in the context of respiratory support and highlighted that the greatest benefit of TCZ might be seen in patients already receiving corticosteroids (54). In addition to the mentioned studies, trials like BACC Bay TCZ Trial and MARIPOSA also contributed to understanding patient selection for TCZ therapy (64, 65). BACC Bay TCZ Trial focused on patients with severe COVID-19 pneumonia and showed a significant reduction in the risk of progression to severe respiratory failure or death (64). MARIPOSA, a randomized, double-blind, placebo-controlled study, investigated the efficacy of TCZ in patients with non-critical COVID-19 pneumonia and did not show significant clinical improvement compared to placebo (65).

These studies emphasize the need for personalized and careful patient selection for TCZ therapy, considering the specificities of the disease, severity of the condition, inflammatory levels, and other relevant factors (51, 54, 62-65). The combination of biomarkers, clinical parameters, and respiratory support plays a crucial role in decision-making to achieve optimal clinical outcomes (51, 54, 62-65).

TCZ AND CORTICOSTEROID SYNERGY

The mechanisms of synergy are intricate and involve the immunosuppressive effects of corticosteroids, such as dexamethasone, inhibiting the immune response (66-70). The combination of these characteristics with the specific IL-6 inhibitor, such as TCZ, leads to a deeper impact in controlling the cytokine storm and reducing hyperinflammation (67, 68). A coordinated approach to these mechanisms becomes crucial for successfully addressing severe forms of COVID-19. Corticosteroid dosage plays a pivotal role in achieving synergy (70). Dose individualization, especially of dexamethasone, enables precise control of inflammation without a significant risk of adverse effects (69). Preliminary data indicate that optimal dexamethasone dosage, in combination with TCZ, may result in a reduction in mortality of up to 30% compared to monotherapy (69).

Research results also suggest a similar mortality benefit between patients treated exclusively with TCZ and those receiving combination therapy (66-70). For instance, patients who received a combination of these medications had a 15% lower mortality rate compared to those who received TCZ alone (68). However, simultaneously, an increased risk of infections, especially fungal and viral, is observed. Preliminary data show that the risk of these infections increases by 20% in patients receiving combination therapy compared to those using TCZ alone (68). Hence, careful risk-benefit evaluation becomes crucial in making dosage decisions.

TCZ AND OTHER MEDICATIONS

One crucial combination involves pairing TCZ with remdesivir, an antiviral medication targeting virus replication (71). TCZ, as an IL-6 inhibitor, intervenes in the proinflammatory response, while remdesivir directly targets the virus. This combination has the potential to act selectively on both the virus and the pathological host response (71-73).

In combination with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or diclofenac, TCZ may enhance anti-inflammatory effects, reducing inflammation symptoms (74). This is particularly significant in controlling the cytokine storm characteristic of severe COVID-19 cases (74). Moreover, the use of anticoagulants in combination with TCZ can significantly reduce the risk of thrombosis, a common occurrence in severe cases of the disease (75-77). The interaction between these drugs can effectively target the coagulation system, mitigating hypercoagulability (75). Combining it with remdesivir can further block vital steps in viral replication, while combining it with NSAIDs can intervene in inflammation-related signaling pathways.

TCZ has also demonstrated interactions with other drugs through liver enzyme systems (49, 50). For instance, studies have shown no clinically significant impact on the exposure of methotrexate, but caution is needed when combining it with statins like simvastatin, as it may affect the blood levels of these drugs (50). It is important to note that drug combinations come with certain risks, including potential interactions and adverse effects (49). Therefore, precise dosing, monitoring of laboratory parameters, and individualized therapy are crucial elements for the successful implementation of such therapeutic strategies (50). These findings provide a foundation for further consideration and adaptation of therapeutic protocols in the treatment of COVID-19, particularly considering the individual characteristics of patients and the specifics of the disease (49, 50).

TCZ IN COVID-19: PATIENTS FROM SERBIA

In the context of TCZ therapy for COVID-19 in Serbia, the available evidence presents a nuanced picture of its efficacy and outcomes. In a retrospective study evaluating TCZ in COVID-19 treatment, distinct observations emerge. The study, involving 205 patients with severe pneumonia, highlights positive outcomes (78). TCZ, administered alongside corticosteroids, led to a significant decrease in CRP and IL-6 levels, with notable improvements in oxygen support requirements. However, a mortality rate of 18.5% among severely ill patients suggests ongoing challenges (78).

A closer examination reveals that the first study, involving 205 patients with severe pneumonia, offers distinct advantages over the second, particularly when considering the unique context of experiences in Serbia. A notable strength of the first study lies in its substantial sample size, involving 205 patients. This larger cohort, especially relevant in the Serbian context, provides a more robust dataset for analysis, potentially offering insights into how TCZ may impact a diverse patient population.

In the second study, the focus was on complications in COVID-19, specifically ARDS and CRS (79). The study conducted a retrospective observational analysis of 92 severe COVID-19 pneumonia patients in Serbia who received tocilizumab in addition to standard therapy (80). The results indicated that patients receiving conventional oxygen therapy before tocilizumab showed a significant decrease in respiratory support after treatment, suggesting a potential beneficial effect (80). Notably, patients requiring high-flow oxygen therapy before tocilizumab treatment had a higher mortality risk compared to those on conventional oxygen therapy (79).

As for the third study, a case presentation involved a male patient with COVID-19 and bilateral pneumonia, who also had psoriasis vulgaris (80). Tocilizumab was administered due to disease progression, and a notable observation was the retreat of psoriatic lesions after tocilizumab administration (80). Despite reports of tocilizumab-induced psoriasis, the study suggested that disrupting IL-6 signaling could be a treatment option for psoriasis (80). This case, although singular, adds an intriguing perspective to the potential broader applications of tocilizumab beyond COVID-19 treatment (80).

In summarizing these studies collectively, while the first study offers insights into the general efficacy and challenges of tocilizumab in severe COVID-19 cases in Serbia, the second and third studies provide additional layers of understanding. The second study hints at the potential benefits of tocilizumab in reducing respiratory support requirements, especially in the earlier stages of ARDS and CRS. Meanwhile, the third study introduces a unique case where tocilizumab appears to have had a positive impact not only on COVID-19 but also on a pre-existing dermatological condition.

CONCLUSION

In conclusion, TCZ shows promising results in reducing inflammatory markers and improving oxygen needs in COVID-19 treatment globally. Despite generally good tolerance, caution is warranted, especially in critically ill patients prone to specific side effects. TCZ's effectiveness varies across clinical trials, emphasizing the importance of timely initiation during the inflammatory phase (days 7-10 post-symptoms). A personalized approach, considering biomarkers like CRP, IL-6, and ferritin, is crucial for patient selection. In the broader context, including Serbia, retrospective studies indicate positive outcomes but also challenges in managing severely ill patients. Amidst the TCZ shortage, investigating alternative dosage strategies, such as a pragmatic 400 mg dose, potentially provides a cost-effective option with comparable mortality benefits, despite the absence of a pharmacoeconomic study to support this. The need for further research and continuous patient monitoring remains essential in managing pandemic challenges.

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UPOTREBA TOCILIZUMABA U LEČENJU TEŠKE FORME KOVIDA 19: PREGLED

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Sažetak

Ovaj pregled se bavi terapijskom primenom Tocilizumaba (TCZ) u lečenju Kovida 19, posebno istražujući njegove mehanizme, bezbednosne aspekte, kliničku efikasnost, strategije doziranja i rezultate u srpskom kontekstu. TCZ, koji deluje kao inhibitor IL-6 receptora, suzbija citokinsku oluju koja se javlja u teškim slučajevima, koristeći svoju strukturu i farmakokinetiku. Dok ukupni profil bezbednosti ukazuje na dobru podnošljivost, postoje suptilne zabrinutosti kod kritično obolelih pacijenata u pogledu javljanja retkih komplikacija. Klinička ispitivanja, sa određenim varijacijama, naglašavaju potrebu za pažljivom interpretacijom indikacija i selekcijom pacijenata za terapiju TCZ-om. Trenutni protokoli koji su na snazi u Republici Srbiji preporučuju primenu TCZ-a u dozi od 8 mg/kg telesne težine na osnovu kliničkih parametara i parametara inflamacije, prvenstveno nivoa IL-6. Uvidom u literaturu uočeno je da se doza tokom nestašice TCZ može korigovati na 400 mg u jednoj dozi tokom lečenja teškog Kovida 19. Optimalno vreme za početak terapije podudara se sa fazom povećane inflamacije (7-10 dana nakon pojave simptoma), uz naglasak na izboru pacijenata prema biomarkerima, težini bolesti i potrebi za respiratornom podrškom. Kombinacija TCZ-a sa kortikosteroidima pokazuje smanjenje smrtnosti, uz potrebu za opreznim doziranjem. Potencijalne koristi proizilaze iz kombinacija TCZ-a sa remdesivirom, NSAIL lekovima i antikoagulansima, što zahteva pažljivo doziranje i nadzor. Retrospektivna istraživanja u Srbiji beleže pozitivne rezultate, ističući potencijal TCZ-a u lečenju ozbiljnih slučajeva. Ukratko, TCZ pokazuje obećavajuće rezultate u lečenju Kovida 19, zahtevajući dalja istraživanja i pažljivo praćenje pacijenata, posebno u uslovima ograničenih resursa.

Ključne reči: Tocilizumab, teška forma Kovida 19, efikasnost, bezbednost, iskustva

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