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Clinical experience with tocilizumab in the treatment of pregnant woman with severe COVID-19

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim of the work – to present a case of positive use of tocilizumab in the treatment of pregnant woman with severe COVID-19.

Materials and methods. A self-observation clinical case of severe coronavirus disease (COVID-19) in pregnant K., 40 years old, who was treated at Municipal Non-Profit Enterprise "Regional Infectious Diseases Clinical Hospital" of Zaporizhzhia Regional Council. The patient was treated in accordance with the "Protocol for the provision of medical care for the treatment of coronavirus disease (COVID-19)".

Results. Our own clinical observation demonstrates the formation of severe COVID-19 in a 40-year-old pregnant woman in the second trimester of pregnancy. Combination treatment with glucocorticoids in the presence of oxygen dependence on the 11th day of the disease was ineffective for two days of clinical and laboratory parameters monitoring, which required a decision on the additional appointment of tocilizumab. The development of "cytokine storm" clinical and laboratory signs on the 12th day of the disease was evidenced by the preservation of fever in the range of 37.5–37.8 °C, no regression of oxygen dependence. According to laboratory data, an increase in the severity of lymphopenia as a relative quantity – up to 5 % and absolute quantity – up to 0.5 × 10^9/l, an increase in fibrinogen – up to 5.8 g/l and D-dimer – up to 1.9 ng/ml, high level of C-reactive protein – up to 190 mg/l. These data justify the additional use of tocilizumab, which was administered at a dose of 8 mg/kg in the absence of contraindications. Tocilizumab administration was effective, contributing to oxygen dependence regression and recovery of laboratory parameters within a week.

Conclusions. Our own clinical observation demonstrates the formation of severe COVID-19 in pregnant woman in the second trimester of pregnancy. Due to the ineffectiveness of glucocorticosteroid therapy and the presence of clear clinical and laboratory signs of "cytokine storm" on the 12th day of the disease, the use of tocilizumab was effective, which contributed to the oxygen dependence regression and recovery of laboratory parameters within a week. Treatment of pregnant woman with severe COVID-19 requires adherence to existing protocols.

Key words: coronavirus disease, COVID-19, infectious pregnancy complications, tocilizumab.

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Клінічний досвід застосування тоцилізумабу в лікуванні вагітної з тяжким перебігом COVID-19

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Мета роботи – описати випадок позитивного застосування тоцилізумабу в лікуванні вагітної з тяжким перебігом коронавірусної хвороби COVID-19.

Матеріали та методи. Наведено клінічний випадок власного спостереження тяжкого перебігу коронавірусної хвороби (COVID-19) у вагітної К., 40 років, яка перебувала на лікуванні в КНП «Обласна інфекційна клінічна лікарня» ЗОР. Лікування хворої здійснили згідно з «Протоколом надання медичної допомоги для лікування коронавірусної хвороби (COVID-19)».

Результати. Показано формування тяжкого перебігу COVID-19 у жінки віком 40 років у II триместрі вагітності. Комплексне лікування з застосуванням глюкокортикоїдів у разі виникнення кисневої залежності на 11 добу хвороби виявилося неефективним протягом двох діб спостереження за клініко-лабораторними параметрами; це потребувало розв'язання питання щодо додаткового призначення тоцилізумабу. Про розвиток клініко-лабораторних ознак «цитокінового шторму» на 12 добу хвороби свідчило збереження підвищеної температури тіла в межах 37,5–37,8 °С, відсутність регресії кисневої залежності. За результатами лабораторних досліджень, зафіксували збільшення виразності лімфопенії – і відносної (до 5 %), й абсолютної (до 0,5 × 10^9/л), підвищення фібриногену – до 5,8 г/л, D-димеру – до 1,9 нг/мл, високий рівень С-реактивного протеїну – до 190 мг/л. Це підтвердило доцільність додаткового призначення тоцилізумабу, який ввели у дозі 8 мг/кг, протипоказань не було. Введення тоцилізумабу виявилось ефективним, сприяло регресу кисневої залежності та відновленню лабораторних показників протягом тижня.

Висновки. Наведене власне клінічне спостереження демонструє формування тяжкого перебігу COVID-19 у вагітної в II триместрі вагітності. Враховуючи неефективність терапії глюкокортикостероїдами та наявність чітких клініко-лабораторних ознак «цитокінового шторму», введення тоцилізумабу на 12 добу хвороби було ефективним, сприяло регресу кисневої залежності та відновленню лабораторних показників протягом тижня. Лікування вагітних із тяжким перебігом COVID-19 потребує чіткого дотримання чинних протоколів.

Ключові слова: коронавірусна хвороба, COVID-19, інфекційні ускладнення вагітності, тоцилізумаб.

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Pregnant women are one of the special and most difficult risk groups for the development of severe and complications of many viral infections. This is due to the formation of certain physiological immunological changes, increased oxygen demand and the emergence of additional risks when medical treatment is required [1]. In the conditions of the coronavirus disease (COVID-19) pandemic, attention was paid to cases of severe and critical course of COVID-19 in pregnant women, especially in the third trimester of pregnancy, with fatal outcome [2,3].

At present, the issue of pregnant patients with COVID-19 treatment remains difficult. In completed and ongoing clinical trials of COVID-19 drug therapy, pregnancy is still usually the exclusion criterion. This significantly limits the development of appropriate guidelines for the pregnant women treatment with this infection. Only the RECOVERY trial, which aimed to determine the appropriateness of dexamethasone in the treatment of patients with COVID-19, included pregnant patients with COVID-19 [4]. According to the results of this study, the minimum effective dose of dexamethasone is 6 mg per day. The inclusion of this drug in the treatment of patients with COVID-19, who need oxygen support, has reduced the mortality of these patients, and there have been no adverse effects associated with pregnancy [4].

Treatment of pregnant COVID-19 patients with severe and critical disease remains an extremely difficult issue. At present, there are no separate protocols for the provision of medical care to this category of patients, so the treatment of pregnant women with severe and critical COVID-19 requires compliance with existing protocols in the country [5,6] and a multidisciplinary approach involving physicians of different profiles [7].

The study of the pathogenetic mechanisms of the formation of the adverse course of COVID-19 demonstrates the leading role of immune-dependent mechanisms with cytokine dysregulation. This allows to justify the feasibility of cytokine-targeted therapy [8]. Such treatment options for patients with severe and critical COVID-19 are the use of interleukin-6 receptor inhibitors (IL-6) (tocilizumab) or IL-1β (anakinra), which are used to treat rheumatoid arthritis [9,10]. Tocilizumab was added as an adjunct to glucocorticosteroid therapy in patients with severe and critical COVID-19 case who have rapid respiratory decompensation. This is in line with existing international recommendations [11,12] and the "Protocol for the provision of medical care for the treatment of coronavirus disease (COVID-19)", approved by the Order of the Ministry of Health (MOH) of Ukraine [6].

Data from the current literature on the effectiveness of tocilizumab in clinical practice have some differences. On the one hand, many studies and meta-analyzes have shown a reduction in mortality among patients with COVID-19 treated with tocilizumab and maintenance therapy [13,14]. On the other hand, there are studies that, on the contrary, have shown no advantages in the results of treatment with tocilizumab in hospitalized patients with COVID-19 [15]. Therefore, clinical and laboratory evaluation of the immunotropic treatment effectiveness with tocilizumab remains relevant today [16]. In our opinion, this is especially true for certain categories of patients with COVID-19 who have risk factors in the form of comorbid conditions, in the pathogenetic mechanisms of which immunological changes are leading [17,18]. There is already a clear pathogenetic justification and successful experience in the literature on the use of tocilizumab in the treatment of patients with severe COVID-19 on the background of comorbid rheumatoid arthritis [18]. Tocilizumab in the treatment of pregnant women with severe and critical course of COVID-19, according to researchers [19], deserves special attention. Blockade of interleukin-6 during pregnancy is of particular interest given the pathophysiological relationship between elevated interleukin-6 levels and preterm birth [20]. Therefore, this led to the feasibility of analyzing their own clinical experience with tocilizumab in the treatment of pregnant women with severe COVID-19.

Aim

The aim of the work – to present a case of positive use of tocilizumab in the treatment of pregnant women with severe COVID-19.

Materials and methods

The clinical case of severe COVID-19 in pregnant K., 40 years old was analyzed. The patient was treated at the Municipal non-profit enterprise "Regional Infectious Diseases Clinical Hospital" of Zaporizhzhia Regional Council (infectious diseases hospital) from 01.10.2021 to 11.10.2021. The diagnosis of COVID-19 was laboratory confirmed by RNA-SARS-CoV-2 in the nasopharynx mucus by polymerase chain reaction. The patient was treated according to the "Protocol for the provision of medical care for the treatment of coronavirus disease (COVID-19)" [6].

Results

Patient K., 40 years old, was admitted to infectious diseases hospital on 01.10.2021 on the 12th day of illness with complaints of fever up to 37.5 °C, nonproductive cough, weakness, shortness of breath during exercise.

The patient had her first pregnancy with a gestational age of 19–20 weeks.

From the anamnesis of the disease it became known that she was not vaccinated against COVID-19. Patient felt ill on 19.09.2021 with an increase in body temperature to 37.5 °C, weakness, the appearance of a liquid dry cough. She was consulted by a family doctor, and RNA-SARS-CoV-2 was isolated from the nasopharyngeal mucus during the polymerase chain reaction. There was outpatient therapy with symptomatic drugs. Against the background of this treatment there was subfebrile persistence.

From 30.09.21 (the 11th day of illness) there was a deterioration: the body temperature rose to 38.0 °C, there were shortness of breath 24 per minute, decreased oxygen saturation to 89 %. In this regard, she was hospitalized in the central hospital of Melitopol. The patient's condition on admission was considered severe due to endogenous intoxication and the appearance of acute respiratory failure. Oxygen therapy in a mask mode was started. Against this background, oxygen saturation in-

creased to 97 %. Radiologically, bilateral polysegmental pneumonia was detected. The general analysis of blood revealed leukocytosis, neutrophilia, relative and absolute lymphopenia: leukocytes – 13.2 × 10^9/l, metamyelocytes – 1 %, stabs – 18 %, segmented – 70 %, lymphocytes – 5 % (abs – 0.6 × 10^9/l), monocytes – 4 %. The results of biochemical tests: prothrombin index – 87 %, fibrinogen – 4.7 g/l, D-dimer – 0.91 ng/ml, blood creatinine – 63 μmol/l, glucose – 3.0 mmol/l. Drug treatment was prescribed: dexamethasone 12 mg per day, low molecular weight heparin in a prophylactic dose, antibacterial therapy with meropenem. However, for two days there was no positive dynamics of clinical manifestations of the disease, in connection with which in the evening of 01.10.2021 the patient was transferred to the infectious diseases hospital.

Upon admission to the infectious hospital on the 12th day of the disease, the patient's condition is severe, body temperature 37.8 °C, respiratory rate 26 per minute, tachycardia 108 per minute, blood pressure 130/80 mm Hg, oxygen saturation 89 % without oxygen support. Oxygen therapy in a mask mode of 12 l/min started immediately, oxygen saturation with oxygen support of 97 %. Auscultatory breathing is weakened on both sides, crepitation is heard. Evaluation of the dynamics of clinical and laboratory parameters on the background of treatment with glucocorticosteroids for two days showed no effect from the prescribed treatment. This was evidenced by the preservation of body temperature in the range of 37.5–37.8 °C, no regression of oxygen dependence, according to laboratory data from 02.10.2021, there was an increase in the severity of lymphopenia as relative – up to 5 % and absolute – up to 0.5 × 10^9/l, increase in fibrinogen – up to 5.8 g/l and D-dimer – up to 1.9 ng/ml, high levels of C-reactive protein – up to 190 mg/l. The above mentioned indicated the development of a "cytokine storm", which became the rationale for the appointment of tocilizumab. According to the results of the follow-up, the level of procalcitonin was 0.1 ng/ml, ALT activity – 26.1 units, creatinine content – 79.7 μmol/l, glucose – 8.6 mmol/l, which indicated the absence of contraindications to the use of tocilizumab. The patient had a body weight of 65 kg at a height of 170 cm (body mass index 22.49 kg/m^2).

Taking into account the above, on 2.10.2021 (the 13th of the disease) 500 mg of tocilizumab (at the rate of 8 mg/kg of body weight) was administered intravenously, dexamethasone was extended, the dose of enoxiparin was doubled, and meropenem was continued. After the use of tocilizumab during the day there was a normalization of body temperature, which was subsequently stable. During the next two days, a significant regression of oxygen dependence was noted, which reduced oxygen support to 4 l/min, which completely disappeared by 8.10.2021. 13 % and absolute – 1.3 × 10^9/l, reduction of fibrinogen – up to 4.1 g/l. Control radiography of the chest from 11.10.2021 showed a clear positive trend in reducing infiltration of lung tissue. On 11.10.2021, the patient was discharged for outpatient treatment with recommendations for continued anticoagulant therapy for two weeks in a prophylactic dose.

Discussion

Literature data indicate that pregnant patients with COVID-19 are more likely to be hospitalized in the intensive care unit than non-pregnant women of the appropriate age [21,22]. A number of studies have identified certain risk factors that affect the severity of COVID-19 in pregnant women. These factors include older age, high body mass index, chronic hypertension, diabetes. The above-mentioned concomitant pathology, which occurred before pregnancy, are factors in the high risk of hospitalization in the intensive care unit and the emergence of indications for artificial lung ventilation [21]. Most researchers point to the fact that a special risk of severe and critical course of COVID-19 occurs in pregnant women in the II and III trimesters, because in the perinatal period or immediately after birth there is an increase in symptoms [23].

Thus, according to the results of American researchers at the time of hospitalization among pregnant women infected with SARS-CoV-2, 61.4 % had an asymptomatic course of COVID-19. However, the onset of labor pains to the appearance we can see different courses of disease: mild clinical symptoms – in 26.5 %, severe – in 26.1 %, and in 5 % – even a critical course of COVID-19 [23]. Our own clinical observation also demonstrates the formation of severe COVID-19 during the second trimester of pregnancy in a pregnant woman, who had one of the risk factors for severe COVID-19, namely the age of the patient 40 years.

Oxygen therapy is given special attention when providing medical care to pregnant women with severe and critical COVID-19. To improve its effectiveness, a prone-positioning algorithm has been developed and recommended for use in clinical practice [7]. In this case, childbirth can be considered as a component of the treatment of refractory hypoxemic respiratory failure in the development of critical conditions of pregnant women, especially during pregnancy 32 weeks and more [7]. At the same time, considerable attention is paid to resolving the issue of prescribing medical treatment. In the current literature, some clinical observations of the treatment of pregnant women with COVID-19 with the use of tocilizumab are currently demonstrated [19]. Our clinical observations also show that with clear clinical and laboratory signs of a cytokine storm on the 12th day of the disease, the use of tocilizumab was effective, leading to regression of oxygen dependence and recovery of laboratory parameters within a week.

Clinical observations on the efficacy of tocilizumab in the treatment of pregnant women with severe COVID-19 are accumulating in the current literature. However, this does not allow definitive conclusions to be drawn regarding the use of these drugs in pregnant women with COVID-19. Therefore, there is an urgent need to include pregnant women in randomized controlled trials to determine the most effective treatments for severe COVID-19 [19,24]. However, in the absence of such studies and specialized protocols for the provision of medical care to pregnant women with COVID-19, the existing Coronavirus Disease (COVID-19) Treatment Guidelines in existing countries should be strictly adhered to.

Conclusions

Own clinical observation showing the formation of severe COVID-19 in pregnant women in the second trimester of pregnancy was presented. Combination treatment with glucocorticoids in the event of oxygen dependence on the 11th day of the disease was ineffective for two days of clinical and laboratory parameters monitoring, which required a decision on the additional appointment of tocilizumab. In the presence of clear clinical and laboratory signs of "cytokine storm" on the 12th day of illness, the using of tocilizumab was effective, which led to the regression of oxygen dependence and the restoration of laboratory parameters within a week. Treatment of pregnant women with severe COVID-19 requires strict adherence to existing protocols.

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