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Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study

Inés Jiménez-Lozano PharmD[1] | José Manuel Caro-Teller PharmD[2] | Nuria Fernández-Hidalgo MD, MSc, PhD[3] | Marta Miarons PharmD, PhD[1] | Marie Antoinette Frick MD[3] | Emma Batllori Badia MD[4] | Berta Serrano MD[5] | Carlos Javier Parramon-Teixidó PharmD[1] | Fátima Camba-Longueira MD[6] | Maria Teresa Moral-Pumarega MD, PhD[4] | Rafael San Juan-Garrido MD, PhD[7] | Maria Josep Cabañas Poy PharmD[1] | Anna Suy MD, PhD[5] | Maria Queralt Gorgas Torner PharmD, PhD[1]

[1]Pharmacy Department, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

[2]Pharmacy Department. Hospital, Universitario "12 de Octubre", Research Institute 12 de Octubre (i+12, Madrid, Spain

[3]Pediatric Infectious Diseases and Primary Immunodeficiencies Unit, Pediatrics Department, Vall d´hebron Hospital, Barcelona, Spain

[4]Unit of perinatal medicine, Obstetric and Gynaecology Department, Hospital Universitario "12 de Octubre", Research Institute 12 de Octubre (i+12, Madrid, Spain

[5]Department of Obstetrics and Gynecology, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

[6]Department of Neonatology, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

[7]Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Research Institute 12 de Octubre (i+12, Madrid, Spain

Correspondence
Carlos Javier Parramon-Teixidó, Pharmacy Department, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus. Passeig Vall Hebron 119-129. Barcelona, Spain.
Email: cparramon@vhebron.net

Abstract

What is known and objective: Tocilizumab is an IL-6 receptor inhibitor agent which has been proposed as a candidate to stop the inflammatory phase of infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, safety data of tocilizumab in pregnant women and their newborn are scarce. We aimed to describe maternal and neonatal safety outcomes associated with tocilizumab treatment in pregnant women with severe COVID-19.

Methods: This is a retrospective study of severe COVID-19 pregnant women, treated with tocilizumab in two Spanish hospitals between 1 March and 31 April 2020. Demographics, medical history, clinical and radiologic findings, treatment information and laboratory data of mothers and their newborns were collected from electronic medical records.

Results and discussion: A total of 12 pregnant women were identified to have received tocilizumab during pregnancy in the two hospitals. Median gestational age at admission was 27.7 weeks (interquartile range, 18.0–36.4). Most of them received lopinavir/ritonavir, azithromycin and hydroxychloroquine, two patients received corticosteroids and one received interferon beta 1B. All 12 pregnancies resulted in live births. Somatometric values were normal for all newborns, and evolution at 14 and 28 days was favourable for all of them. Hepatotoxicity was observed in 2 patients, which improved or resolved at discharge. Cytomegalovirus reactivation was detected in another patient who had also received corticosteroids for 15 days, causing a congenital infection in her newborn. Both hepatotoxicity and viral reactivation adverse events were classified as possibly related to tocilizumab administration according to Naranjo's causality algorithm.

Anna Suy and, Maria Queralt Gorgas Torner contributed equally.

What is new and conclusions: It does not appear that tocilizumab has detrimental effects for the mother and newborn. Close monitoring of infections should be considered, especially if other immunosuppressive agents are used.

KEYWORDS
adverse events, COVID-19, maternal safety, newborn safety, tocilizumab

1 | WHAT IS KNOWN AND OBJECTIVE

Coronavirus disease-2019 (COVID-19) is a highly infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Data from approximately 400,000 symptomatic women of reproductive age with confirmed SARS-CoV-2 infection, have shown that pregnant women are more likely to be admitted to the intensive care unit (ICU), to receive invasive ventilation or extracorporeal membrane oxygenation, or to die, in comparison with nonpregnant women.[2]

Anatomical and hormonal changes might contribute to pregnant women susceptibility to respiratory pathogens, therefore SARS-CoV-2.[3–5] COVID-19-associated systemic inflammation and hypoxic respiratory failure have been linked to an increased cytokine release, as indicated by elevated blood levels of interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer, and ferritin.[6] Based on the knowledge that pregnant women in their first and third trimester are at a pro-inflammatory state, the cytokine-storm induced by SARS-CoV-2 may prompt a more severe inflammatory state.[7]

Tocilizumab is an IL-6 receptor inhibitor agent which has been proposed as a candidate to stop the inflammatory phase of infection by SARS-CoV-2. However, there are conflicting efficacy data between observational studies and randomized clinical trials, thus its routine use in most COVID-19 settings cannot be recommended.[8] Moreover, safety data of tocilizumab in pregnant women are scarce[9] and there is a lack of evidence of its use in COVID-19 pregnant patients.

Due to the limited evidence of the use of tocilizumab in pregnant women, we aimed to describe safety maternal and neonatal outcomes associated with tocilizumab treatment in pregnant women with severe COVID-19.

2 | METHODS

2.1 | Setting for the study and subjects

We conducted a retrospective study of pregnant woman treated with tocilizumab for COVID-19 between March 1 to April 31 2020, at two tertiary Spanish hospitals, the Vall d'Hebron University Hospital, Barcelona and the 12 de Octubre University Hospital, Madrid. A laboratory-confirmed case was defined as a patient with a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) SARS-CoV-2-positive result in any respiratory sample. The date of onset of disease was defined as the day when the symptoms were first noticed.

2.2 | Outcomes

The main outcome was adverse drug events (ADEs) related to tocilizumab administration in pregnant women and their offspring. Secondary outcomes were maternal and perinatal outcomes.

2.3 | Standard of care and tocilizumab administration

Treatment with oral lopinavir/ritonavir, azithromycin and hydroxychloroquine was initiated following clinical practice guidelines for COVID-19 proposed by the Spanish Ministry of Health[10] and local protocols adapted to each centre. After subsequent protocols' amendment, lopinavir/ritonavir was removed in 12 de Octubre Hospital from mid-April onwards, and azithromycin was removed from the last week of April onwards in Vall d'Hebron Hospital. Subcutaneous interferon beta 1B (IFN β-1B) was used at the beginning of the pandemic if unfavourable evolution because of a potential role in reducing SARS complications. Intravenous tocilizumab was considered in patients that fulfilled the following criteria in both hospitals: (1) bilateral pulmonary infiltrates or radiological and/or gasometric worsening in 24 h in hospitalized patients; (2) respiratory failure; (3) IL-6 levels ≥40 ng/L (or PCR ≥ 100 mg/L) and/or D-dimer levels ≥1000 ng/ml and/or ferritin ≥700 ng/ml. When IL-6 levels were not available, the clinic criterion was used to start tocilizumab. Initially, a 600 mg dose of tocilizumab followed by a second infusion of 600 mg (in patients weighing ≥80 kg) or 400 mg (in patients weighting <80 kg) with an interval of 12 h between both doses was considered. After Spanish protocol amendment in mid-March, a 600 mg dose was established to patients weighing >75 kg, otherwise 400 mg. A second equal dose was considered in patients with a poor early response.

2.4 | Data collection

We retrospectively collected sociodemographic characteristics, past medical and obstetric history, usual medication, gestational age and current obstetric pathology. Laboratory and radiologic findings, vital signs and symptoms, microbiological tests others than SARS-CoV-2

RT-PCR on respiratory samples, clinical signs or symptoms, treatment and supportive measures needed and ADEs were evaluated at admission, at 48 h and weekly during hospital admission. Maternal and foetal outcomes were obtained from patients' medical records. Gestational age at pregnancy termination and type of labour were also collected. Neonatal SARS-CoV-2 nasopharyngeal aspirate samples, somatometric evaluation including weight, length and head circumference, neonatal ICU admission and follow-up at 14 and 28 days were also collected. Data were recorded in the Research Electronic Data Capture software (REDCap, Vanderbilt University). The date of data cut-off for outcomes was 30 September 2020, to allow 28 days follow-up for all newborns.

2.5 | ADEs evaluation

ADEs cause-effect relationship was evaluated using the Naranjo's algorithm.[11] Briefly, this questionnaire is one of the more commonly used algorithms for determining the likelihood of whether an adverse drug reaction is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful, avoiding data omissions or inaccuracy among evaluators.[12,13]

2.6 | Statistical analysis

Descriptive characteristics were calculated for the variables of interest. Continuous variables were expressed median and range. Categorical variables were summarized as absolute number and relative frequencies.

3 | RESULTS AND DISCUSSION

The study included 12 COVID-19 pregnant women, 6 from of Vall d'Hebron University Hospital (of 49 admitted) and 6 from of 12 de Octubre Hospital (of 38 admitted). Median (range) age and gestational age at admission were 37 (23–50) years and 27.7 (18.0–36.4) weeks, respectively. One patient had an increased uterine artery resistance index, and two patients had gestational diabetes. Baseline analytical characteristics at admission are shown in Table 1.

Median hospital length of stay was 11.5 (7–42) days. Oxygen support was required in all 12 patients; seven (58%) of them required high flow oxygen, two (17%) required noninvasive ventilation and 3 (25%) required invasive mechanical ventilation (these last 3 patients for 2, 8 and 21 days, respectively). Five patients were admitted to ICU due to acute respiratory failure, with a median stay of 6 days (2–27 days).

Eight of 12 patients (66.7%) received lopinavir/ritonavir, azithromycin and hydroxychloroquine. Azithromycin was omitted in the other 4 patients and lopinavir-ritonavir in 3 of these 4 patients, as per protocol's amendments during the study period. Lopinavir/ritonavir was discontinued early in 3 patients due to diarrhoea and in 1 patient due to vomiting. Empiric antibiotic therapy was initially added to 10 patients (ceftriaxone in 7; cefuroxime in 1; amoxicillin-clavulanate in 1; levofloxacin in 1) due to bacterial superinfection suspicion. One

TABLE 1 Laboratory findings and vital signs at admission of COVID-19 pregnant women included

	Patient number											
	1	2	3	4	5	6	7	8	9	10	11	12
Analytical data												
Leucocytes (×10^9/L)	14.6	4.6	8.9	12.1	12.0	9.2	7.4	10.9	8.3	8.2	5.8	10.2
Platelet (×10^9/L)	213	142	505	247	336	189	190	242	316	164	221	171
CRP (mg/L)	12.3	4.3	10.1	17.6	11.8	26.6	8.8	12.7	6.3	8.0	5.9	11.6
IL–6 (ng/L)	287.9	76.5	39.6	42.6	86.2	59.7	21.0	3.0	-	-	-	-
D-Dimer (ng/mL)	617	576	397	554	412	810	-	-	960	-	-	-
Ferritin (ng/mL)	160	220	230	150	102	383	370	569	-	-	-	-
Fibrinogen (g/dL)	0.57	0.38	0.65	0.64	0.66	0.69	0.71	-	0.5	0.5	0.8	-
LDH (UI/L)	380	342	251	291	415	300	374	301	211	268	231	368
Vital signs												
Oxygen Saturation (%)	97	92	96	94	100	98	95	95	100	99	90	91
Respiratory rate (BrPM)	23	26	30	36	32	18	22	22	32	24	38	-
Heart rate (BPM)	116	82	111	99	115	114	111	87	113	100	102	101
SBP (mmHg)	135	116	113	113	110	116	93	85	119	100	108	116
DBP (mmHg)	80	63	67	74	70	80	58	48	64	54	64	43

Abbreviations: BPM, Beats per minute; BrPM, Breaths per minute; CRP, C-reactive protein; DBP, Diastolic Blood Pressure; IL-6, Interleukin 6; LDH, Lactate dehydrogenase; SBP, Systolic Blood Pressure.

patient received IFN β-1B. All patients received thromboprophylaxis with low-molecular-weight heparin at standard (*n* = 11) or high prophylaxis doses (*n* = 1). Two patients received methylprednisolone, for 3 and 15 days, respectively.

Tocilizumab dosing, and respiratory and analytical data immediately before tocilizumab administration are shown in Table 2. Eight patients (67%) received a single dose of tocilizumab and 4 (33%) received two doses. Dosing followed current protocol in all patients but 1, which was above 75 kg and received 400 mg of tocilizumab (no specified reasons). Analytical data before and after tocilizumab dosing are shown in Figure 1.

All 12 pregnancies resulted in live births. Median gestational age at delivery was 38.9 weeks (27.7–40.6). Ten patients (83.3%) were discharged before delivery due to COVID-19 improvement and were admitted subsequently for pregnancy termination. Caesarean section was performed in 7 patients due to urgent maternal conditions (2), prolonged labour (1) or elective caesarean (4).

Cytomegalovirus (CMV) reactivation was detected in 1 patient that received tocilizumab 8 days after admission, when performing viral screening due to liver enzyme alteration. This patient also received a cumulative dose of 1.156 mg of methylprednisolone during 15 days. Analytical and serology data are shown in Figure 2. This patient also presented skin lesions on the left thigh compatible with fungal infection 22 days after admission, and a persistent bacteriuria.

Cytolytic hepatotoxicity was observed in 2 patients. Evolution of hepatic parameters is shown in Figure 3. Follow-up allowed confirming levels' normalization in one patient before discharge, and the other had a downward trend at discharge.

According to Naranjo's causality algorithm, both CMV reactivation and hepatotoxicity adverse events were classified as possibly related to tocilizumab administration.

All 12 neonates were tested at birth for SARS-CoV-2 by RT-PCR of nasopharyngeal aspirate, which were all negative. Somatometric values were all normal and the evolution at 14 and 28 days was favourable for all newborns.

Two newborns were preterm; one was a late preterm of 36.6 gestational weeks who was initially admitted at ICU due to maternal conditions, and the other was a 28 gestational weeks' newborn who required urgent caesarean section due to unfavourable maternal evolution. She evolved favourably at 28 days follow up. Nevertheless, she presented common preterm pathology such as hyaline membrane disease, apnoea of prematurity, patent ductus arteriosus, neonatal anaemia, non-isoimmune jaundice, parenchymal brain injury grade 1, mild respiratory tract viral infection and *Klebsiella pneumoniae* conjunctivitis.

Another newborn was diagnosed of cleft lip and palate at gestational week 20, and it was therefore confirmed before maternal COVID-19 at gestational week 27. Finally, a congenital CMV was confirmed by urine and blood determinations to the newborn whose mother had the CMV reactivation. She received antiviral treatment from birth. Fundus examination, auditory evoked potentials, transfontanellar ultrasound and brain magnetic resonance imaging were normal.

To our knowledge, this is the first report that specifically assesses tocilizumab safety in COVID-19 pregnant women and their offspring. Tocilizumab administration did not seem to have significant detriment to maternal or neonatal health when treating severe COVID-19 pregnant women. However, viral reactivation in one patient was an adverse outcome that should aware healthcare providers about the risk of secondary infections when immunosuppressive agents are used in pregnant women, which can also have consequences in the foetus or newborn.

Serious and sometimes fatal infections, such as bacterial infections and viral reactivation (hepatitis B), are well known adverse events of immunosuppressive agents[9] and recent evidence in COVID-19 patients has also shown this bacterial superinfection risk. In the study by Quartuccio et al.,[14] 42.9% (18/42) of the patients in a tocilizumab retrospective cohort experienced bacterial superinfection, but none in the control group. This was consistent with the study by Kimming et al.[15] in which tocilizumab administration was independently associated with the presence of secondary bacterial infections. In addition, in the study by Morena et al,[16] the most common adverse event was the increase of hepatic enzymes (29%), thrombocytopenia (14%) and serious bacterial and fungal infections (27%). In the report by Toniati et al.[17] involving 100 patients treated with tocilizumab, two patients died due to septic shock and 1 patient had gastrointestinal perforation requiring urgent surgery. However, other authors did not find this increased risk of infection.[18] Nevertheless, there is no conclusive evidence explaining which of these adverse effects were directly related to tocilizumab therapy. Since IL-6 plays a crucial role in B-cell proliferation, antibody production and T-cell differentiation and cytotoxicity, the inhibition of the complex formation with its receptor may trigger the dysfunction of antigen-specific CD8-positive T cells, which is associated with CMV reactivation.[16] In fact, CMV reactivation has been reported previously in a few publications, basically in immunosuppressed patients who were also treated with other immunosuppressive agents, as is the case of our patient, and in some occasions shortly after tocilizumab initiation.[16–22]

Noteworthy, our patient was also treated with methylprednisolone during 15 days, which might add immunosuppressive effects and contribute to viral reactivation. Evidence supports corticosteroids association with viral infections, including CMV, either in immunocompetent or immunocompromised patients.[9,23,24]

The incidence of mild liver injury in hospitalized patients with COVID-19 ranges from 14% to 53%, which is higher in more severe cases.[25] Previous reports have shown similar liver injury (23.8%–44.4%) in COVID-19 pregnant women.[26,27] Mechanisms of liver damage in COVID-19 are still unknown but might be related to direct cytopathic effect of the virus, immune-mediated damage or liver hypoxia induced by a thrombotic context or due to SARS.[25] Drug-induced liver injury is another recognized factor of hepatotoxicity and many drugs that have been used in COVID-19 patients, such as hydroxychloroquine, azithromycin, lopinavir/ritonavir, IFN β and also tocilizumab.[9,25,28] Thus, in our

TABLE 2 Laboratory findings and vital signs of COVID-19 of pregnant women immediately before tocilizumab administration

	Patient number											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
TZ dosing	400 + 400 mg	400 + 400 mg	600 mg	400 mg	600 mg	600 mg	600 + 400 mg	600 + 400 mg	400 mg	600 mg	400 mg	600 mg
Days of hospitalization until TZ administration	1	7	2	0	1	1	1	1	4	6	2	3
Days of symptoms onset before TZ administration	4	13	16	8	11	8	10	12	9	10	7	10
Type of oxygen support and requirements	NC FiO_2 0.5	IMV FiO_2 0.6	HFOD FiO_2 1	HFOD FiO_2 0.31	HFOD FiO_2 0.7	HFOD FiO_2 0.26	NC FiO_2 0.26	NC FiO_2 0.26	HFOD FiO_2 0.51	NC FiO_2 0.36	NC FiO_2 0.3	HFOD FiO2 0.66
Chest examination and radiological findings	Crackles BI	BI	Crackles BI	BI	BI	BI	BI	BI	BI	BI	BI	BI
Analytical data												
Leucocytes ($\times 10^9$/L)	14.6	7.5	9.0	10.9	12.1	9.2	10.9	8.3	6.0	7.9	8	21.1
Platelet ($\times 10^9$/L)	213	225	505	247	260	189	242	316	298	252	259	199
CRP (mg/L)	12.3	24.2	10.5	17.6	11.8	26.6	8.8	12.7	7.2	11.6	10.1	21.8
IL–6 (ng/L)	287	409	40	42.6	86.2	59.1	--	3	31	--	--	56
D-Dimer (ng/mL)	617	5699	397	551	412	810	961	--	1107	757	309	--
Ferritin (ng/mL)	160	258	230	150	102	383	370	569	224	144	--	1526
Fibrinogen (g/dL)	0.57	0.58	0.65	0.64	0.66	0.69	0.73	0.71	0.72	0.65	0.85	0.71
LDH (UI/L)	380	306	251	291	415	300	475	308	271	297	280	649
Vital signs												
Oxygen Saturation (%)	97	92	98	94	100	98	89	97	96	100	97	95
Respiratory rate (BrPM)	23	33	30	36	32	18	28	22	28	28	28	43
Heart rate (BPM)	116	71	93	99	115	114	77	106	100	105	93	89
SBP (mmHg)	135	150	120	113	110	116	104	97	102	97	105	104
DBP (mmHg)	80	76	65	74	70	80	69	67	53	52	65	51

Abbreviations: BI, Bilateral infiltrates; BPM, Beats per minute; BrPM, Breaths per minute; CRP, C-reactive protein; DBP, Diastolic Blood Pressure; FIO2, Fraction of inspired oxygen; HFOD, High Flow Oxygen Device; IL-6, Interleukin 6; IMV, Invasive Mechanical Ventilation; LDH, Lactate dehydrogenase; NC, Nasal Cannulas; SBP, Systolic Blood Pressure; TZ, tocilizumab.

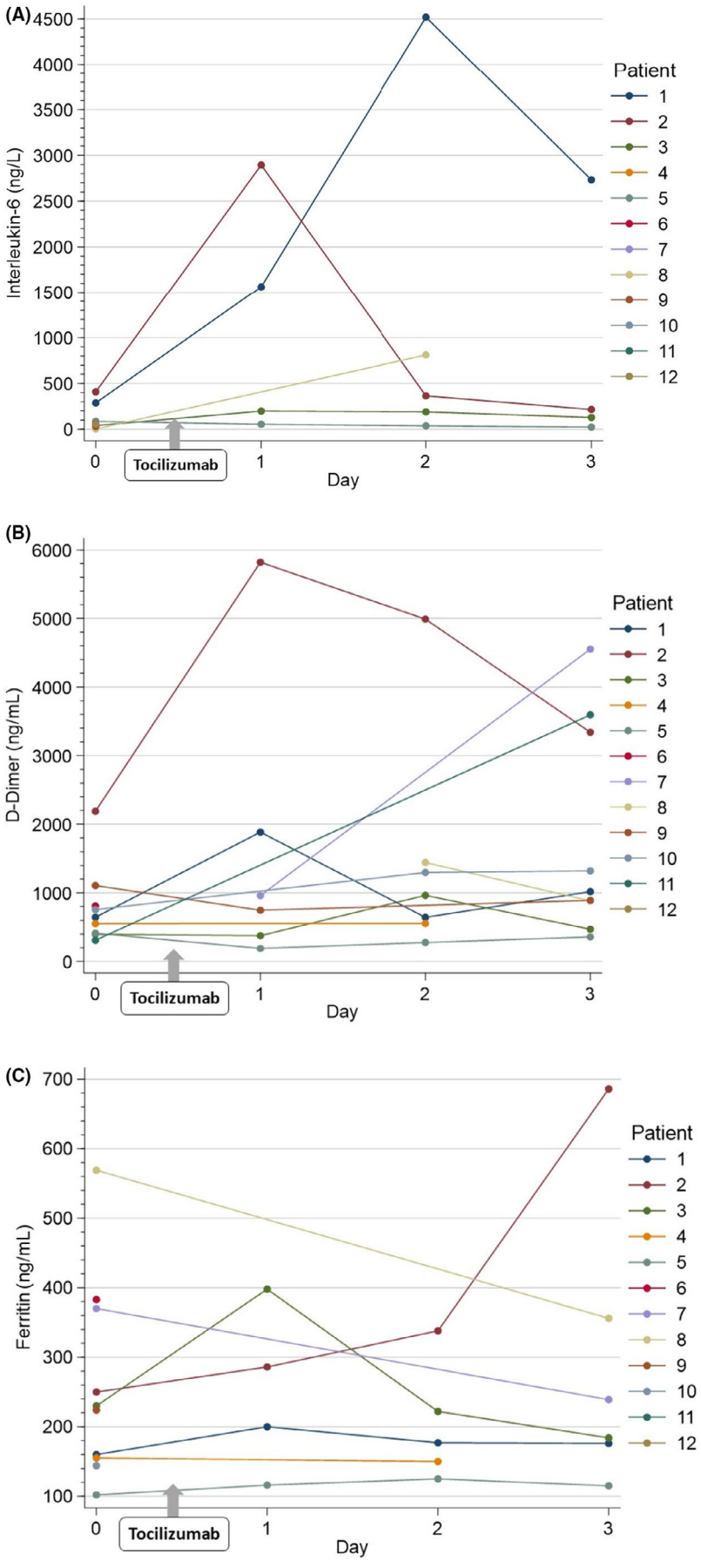

FIGURE 1 Analytical data before and after tocilizumab administration. Evolution of patients' interleukin-6 (Figure 1A), D-Dimer (Figure 1B) and ferritin (Figure 1C) plasma levels per day after tocilizumab administration. Day 0 corresponds to levels of each parameter immediately before tocilizumab administration. (A) Interleukin-6 evolution. (B) D-Dimer evolution. (C) Ferritin evolution

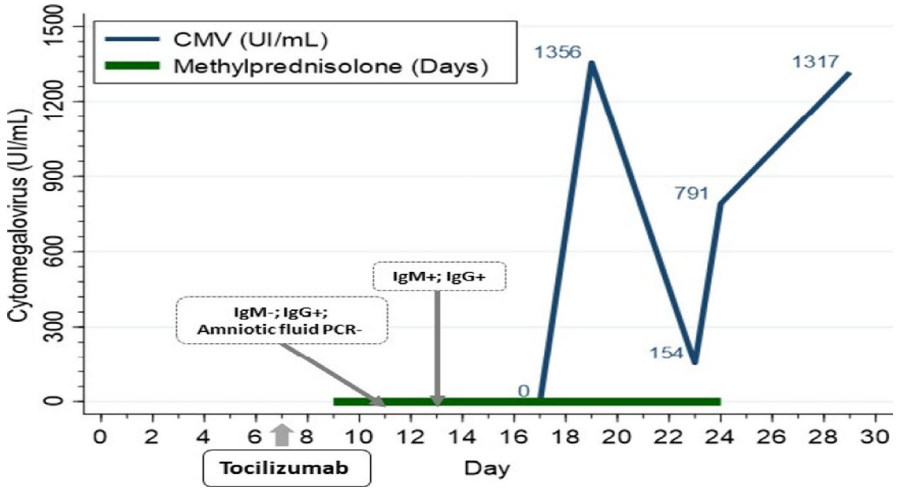

FIGURE 2 Cytomegalovirus evolution. Evolution of cytomegalovirus viral load and serology tests in patient 2. CMV, Cytomegalovirus; IgM, Immunoglobulin M; IgG, Immunoglobulin G; PCR, polymerase-chain-reaction

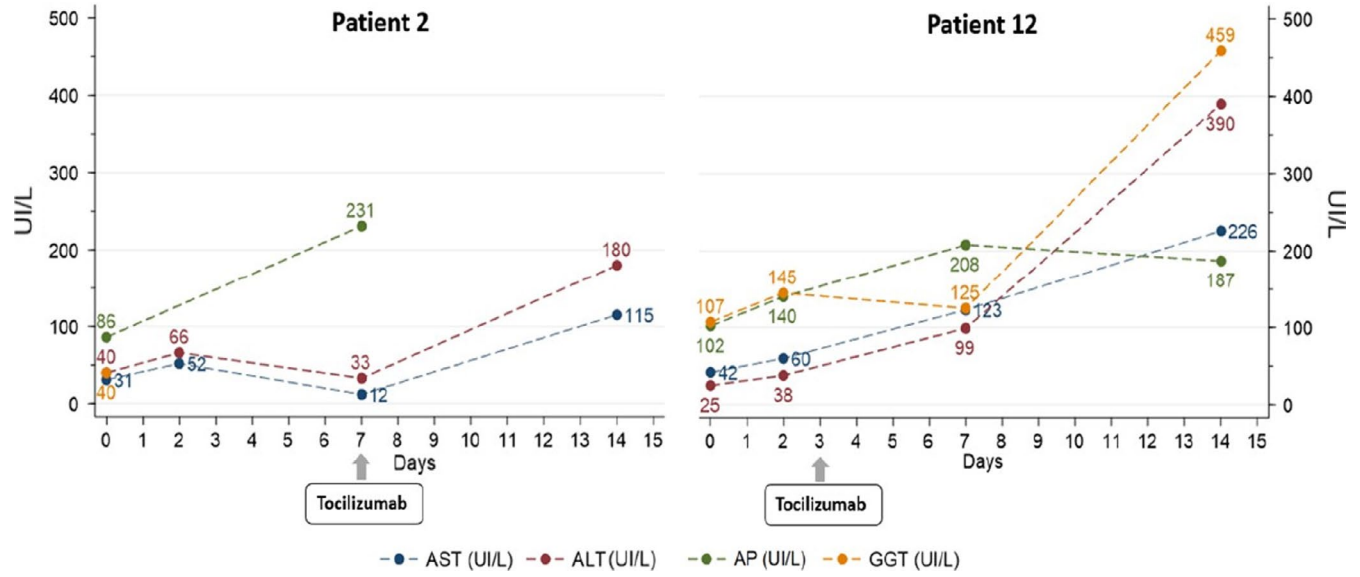

FIGURE 3 Evolution of hepatic parameters. Evolution of hepatic parameters in the two patients in whom hepatic involvement was possibly associated with tocilizumab administration. AST, aspartate aminotransferase; ALT, aspartate aminotransferase; AP, Alkaline phosphatase; GGT, Gamma-glutamyltransferase

study patients received other known hepatotoxic agents which could contribute to the liver injury. It must be highlighted that the observation of these liver laboratory abnormalities in pregnant women along with haemolysis and thrombocytopenia might coincide with those that occur in pre-eclampsia with severe features or HELLP syndrome (haemolysis, elevated liver enzymes, low platelets); thus, it might be distinguished with appropriate analytical and clinical assessment.[29]

Regarding foetal toxicity, available preclinical data have shown no special risk for humans based on conventional studies of safety, repeated dose toxicity and genotoxicity. However, an increased risk of spontaneous abortion/embryo-foetal death was proven in cynomolgus monkeys during early gestation at high doses (> 100 x human exposure). Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.[9] In a review by *Hoeltzenbein* et al., data from clinical trials and post-marketing data suggested that tocilizumab administration did not substantially increase risk for malformations after exposure shortly before conception or early in the first trimester.[30] However, an increased rate of preterm birth and low birth weight children was observed in pregnant patients with rheumatoid arthritis. Of the patients exposed in the second and third trimesters, an incidence of premature birth was observed in 6 of 17 neonates and a low birth weight (<2500 g) in 4 of 17 neonates. Although it cannot be ruled out that tocilizumab exposure contributes to this risk, the poor control of the disease (measured by the increase in IL-6 and IL-18) has also been associated with worse results in terms of foetal abnormalities, preterm birth and low birth weight. Retrospective data from another report showed no increased rates of spontaneous abortion or congenital abnormalities in 61 patients with rheumatic disease exposed to tocilizumab.[31]

We did not observe any congenital malformation, apart of the cleft lip and palate in one foetus, which was diagnosed before COVID-19 and tocilizumab treatment in the mother. CMV congenital infection in the newborn whose mother had CMV reactivation reveals the risk of vertical transmission in previously CMV immune pregnant women, although the severity of the infection tends to be less and is usually asymptomatic for both mother and newborn.[32]

The potential role of tocilizumab in COVID-19 patients is still uncertain. Available observational studies reported clinical benefit by showing a reduction of invasive mechanical ventilation or death.[9,33,34] Nevertheless, limitations of these heterogeneous studies are evident insofar as they included patients with different severity, different dosing schemes, and most had small sample sizes. Newly released randomized clinical trials (RCT) do not show consistent evidence of this efficacy. CORIMUNO-19-TOCI-1 trial findings suggested that tocilizumab may improve survival without the need for noninvasive or mechanical ventilation by day 14, but no reduced risk of a World Health Organization clinical progression scale (WHO-CPS) score of greater than 5 at day 4 was observed.[35] In the RCT-TCZ-COVID-19 and COVACTA studies, there were no statistically significant differences in death, or in combined outcomes of death, mechanical ventilation or intensive care admission, with tocilizumab compared with placebo or standard care.[36,37] However, the COVACTA study showed reduced hospital lengths of stay in tocilizumab-treated patients.[37] On the other hand, the EMPACTA study reported efficacy in its primary end point, reduction of mechanical ventilation or death by day 28, but there was no statistically significant difference in mortality alone.[38] Finally, the REMAP-CAP preliminary results suggest that tocilizumab is beneficial in adults with severe COVID-19 who are critically ill and receiving respiratory or cardiovascular organ support in an intensive care setting. It should be noted that all these RCT included very different study populations; thus, conclusions should be carefully interpreted.[39]

Although no routine use of tocilizumab for COVID-19 is recommended at this moment, upcoming clinical trials' results might add evidence to ascertain tocilizumab benefits.[9]

3.1 | Strengths and limitations

This study has some limitations. Methodology sample size of the study was small, which precludes definitive conclusions to be reached, but gives preliminary results of ADE related to the use of tocilizumab in pregnant women. Also, co-medication could be a potential confounding factor that might contribute to ADE development. Finally, data inaccuracy inherent to the retrospective use of databases may occur, but careful review of computerized medical records allowed us to accurately evaluate drug exposure and ADE.

4 | WHAT IS NEW AND CONCLUSIONS

Tocilizumab has shown no detrimental effects in COVID-19 pregnant women and their newborns in our setting. Although there was a low risk of secondary infections observed, close monitoring of infections should be considered especially if other immunosuppressive agents are used.

CONFLICT OF INTEREST

All authors report no conflict of interest and are alone responsible for the content and the writing of the article.

ETHICAL APPROVAL

The institutional review board of both centres provided ethical clearance (reference number: VHI-TOC-2020–01), on 19 June 2020 at Vall d'Hebron Hospital and on 6 July 2020 at 12 de Octubre Hospital, and granted a waiver of informed consent due to retrospective data collection.

PATIENT CONSENT STATEMENT

The institutional review board of both centres granted a waiver of informed consent due to retrospective data collection.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Does not apply.

SUBMISSION DECLARATION

This manuscript has not been published previously, neither is not under consideration for publication elsewhere. Its publication is approved by all authors and also by the responsible authorities where the work was carried out, specifically, by Ethics' Committees of both hospitals and Spanish Agency of Medicines and Medical Devices. If the manuscript is accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available within the article.

ORCID

Inés Jiménez-Lozano https://orcid.org/0000-0003-4473-6768
Marta Miarons https://orcid.org/0000-0001-7847-1580
Carlos Javier Parramon-Teixidó https://orcid.org/0000-0001-8023-3979

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