Neuroimmunology Reports 1 (2021) 100014

Contents lists available at ScienceDirect

Neuroimmunology Reports

journal homepage: www.elsevier.com/locate/nerep

# Successful pregnancy and disease outcomes in a NMOSD patient treated with tocilizumab

Marco Capobianco[a,*], Luca Marozio[b], Simona Malucchi[a], Maria Malentacchi[a], Marianna Lo Re[a], Alessandra Coscia[c], Antonio Bertolotto[a]

[a] Department of Neurology and Regional Referral Multiple Sclerosis Centre, University Hospital S. Luigi, Regione Gonzole 10, Orbassano, Italy
[b] Department of Obstetrics and Gynecology, University of Turin Turin, Italy
[c] Department of Neonatology, University of Turin, Turin, Italy

ARTICLE INFO

*Keywords:*
Neuromyelitis optica spectrum disorder
Pregnancy
Tocilizumab

ABSTRACT

*Background:* Neuromyelitis Optica Spectrum Disorder (NMOSD) is an autoimmune relapsing disease involving the central nervous system with predominant inflammatory attack of optic nerves, spinal cord and area postrema, often leading to severe disability. Women with NMOSD typically experience adverse pregnancy outcomes and high relapse rates during pregnancy and the postpartum period.

*Case report:* Herein we present a case of pregnancy in a young NMOSD woman treated with tocilizumab. The course of her pregnancy was clinically unremarkable and treatment whit Tocilizumab was well tolerated.

*Conclusions:* This case raises the possibility that the modulation of immune system by inhibitors of the IL-6 pathway could a promising therapeutic option for pregnancy in NMOSD patient.

## Case report

Written informed consent was received from the patient for describing her case. A 20-year-old woman was diagnosed with NMOSD in 2007 after having experienced acute myelitis involving C4-T3 spinal segments; serum anti-Aquaporin-4 (AQP4) and anti-Myelin Oligodendrocyte Glycoprotein (MOG) antibodies tested negative.

Gilles de la Tourette syndrome was previously diagnosed and treated with low dose tetrabenazine.

Soon after plasma-exchange courses for relapse, she was treated with rituximab using a treatment-to-target strategy, monitoring B-cell counts (CD19+ cells) monthly: redosing was scheduled at CD19+ cells detection in the blood. [Valentino et al., 2016]

She subsequently developed 8 relapses in the next 9 years, mainly involving spinal cord, reaching an EDSS score of 5.5. After the last relapse in feb-2016 she was switched to monthly tocilizumab infusion at the dose of 8 mg/kg with complete control of the disease and improvement of EDSS score at 4.5. No significant adverse events were detected.

After 32 tocilizumab infusions (sep-2018) she accidentally became pregnant and because of the severity of her relapses, the high risk of relapses during pregnancy and after delivery, a physician-patient informed decision was made to continue tocilizumab till the 28$^{th}$ week of gestation (jan-2019), in order to avoid fetal passage of the drug. Tetrabenazine was suspended, too.

Pregnancy course was clinically unremarkable, and she gave birth to a boy at 35 weeks by caesarean section (mar-2019). Birth weight was 2330g and the Appearance, Pulse, Grimace, Activity, Respiration (APGAR) score was 1-2-5 at 1-5-10 minutes. As usually happens in preterm births, the newborn was hospitalized for respiratory failure due to pulmonary surfactant deficiency.

After 7 days he was discharged in good clinical condition. No hematological abnormalities were found (white blood cells count 7560/ml, hemoglobin 14.2 g/l, red blood cells $4.16 \times 10^6$/ml, platelets 338,000/ml).

No developmental anomalies nor hematological and immunological alteration were detected till 1 year of age.

Treatment was well tolerated both during pregnancy and the 2-months washout before delivery, with no signs of infection or clinical signs of relapses.

Four days after delivery, tocilizumab infusions were resumed and the patient did not experience any new relapses or radiological activity till 1 year after delivery (brain and spinal cord MRI were performed at 1-3-6 and 12 months after delivery). Her EDSS score remained stable (Fig. 1).

* Corresponding author at: Department of Neurology and Regional Referral MS Centre, University Hospital S. Luigi, Regione Gonzole 10, Orbassano, Italy
*E-mail addresses:* mcapobianco1972@gmail.com (M. Capobianco), luca.marozio@unito.it (L. Marozio), alessandra.coscia@unito.it (A. Coscia).

https://doi.org/10.1016/j.nerep.2021.100014
Received 7 July 2021; Accepted 6 September 2021

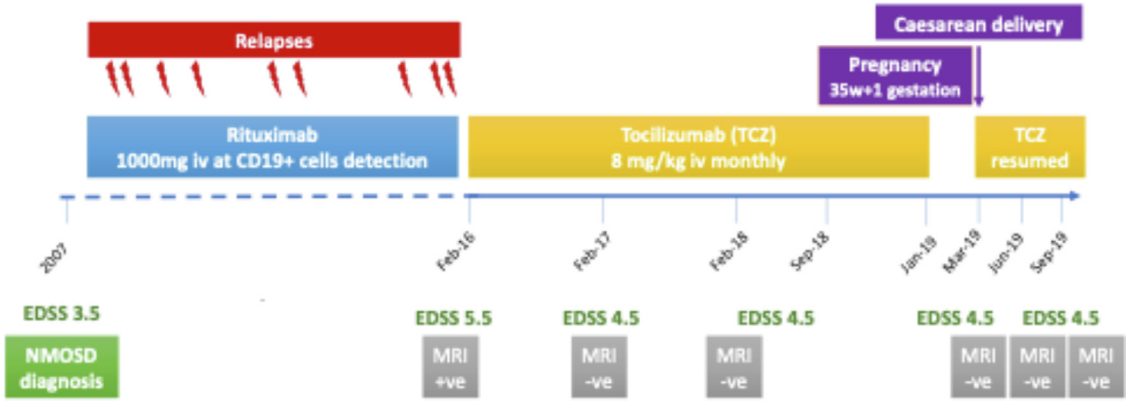


**Fig. 1.** Clinical course of NMOSD in a young woman: several relapses were recorded during rituximab treatment as MRI disease activity (not shown). After switching to tocilizumab no clinical or disease activity were detected even during unexpected pregnancy and in the post-partum period.

## Discussion

As far as we know this is the first report of maternal exposure of tocilizumab in NMOSD. Tocilizumab is an anti IL6-receptor humanized monoclonal antibody used for refractory NMOSD. [Ilya Ayzenberg et al., 2013]

Previous data on tocilizumab and pregnancy were obtained mainly from Rheumatoid Arthritis patients with pregnancy exposure during the first trimester. No concerns arose for both pregnancy outcome and congenital anomalies. [Hoeltzenbein et al., 2016]

Pregnancy course and delivery outcomes in NMOSD are affected by bad outcomes as relapses continue during pregnancy and increase in rate after delivery, furthermore preeclampsia and fetal loss are more frequent in NMOSD than in controls. [Shosha et al., 2017]

Previously pregnancy good outcomes have been described in NMOSD patients exposed to rituximab, but in some cases, NMOSD relapses were recorded postpartum despite undetectable B cells. [Das et al., 2018]

IL-6 upregulation has been described in systemic fetal cytokine response as a major independent risk factor for subsequent development of neonatal morbid events even after adjustments for gestational age and other confounders. [Chiesa et al., 2015]

Our findings could be of importance in determining the treatment strategy based on the age of pregnancy of NMOSD patients, particularly in the near future with the arrival of specific monoclonal antibodies with different target, as eculizumab (anti-complement C9 factor), inebilizumab (anti-CD19 B-cells depleting agent) and satralizumab (anti-IL6 receptor binding both membrane-bound and soluble receptor forms, blocking IL6 signaling pathway). [Huda et al., 2019]

The good outcome of pregnancy, delivery and fetal outcomes under tocilizumab treatment and the possible detrimental effect of IL-6 upregulation on pregnancy itself, suggest that the modulation of immune system by IL-6 pathway inhibitors could be rational in autoimmune aggressive disease such as NMOSD patients coping with pregnancy.

## Declaration of Competing Interest

The authors do not have any specific conflict of interest to be declared regarding the present paper.

An informed consent was obtained by the patient allowing to publish clinical data.

The present paper was not funding.

## Acknowledgement

The authors do not have any specific conflict of interest to be declared regarding the present paper.

## References

Valentino, P, Marnetto, F, Granieri, L, 2016. Aquaporin-4 antibody titration in NMO patients treated with rituximab: A retrospective study. Neurol. Neuroimmunol. Neuroinflamm. 15 (2), e317.

Ilya Ayzenberg, MD, Ingo Kleiter, MD, Schroder, Alexandra, 2013. Interleukin 6 receptor blockade in patients with neuromyelitis optica nonresponsive to anti-CD20 therapy. JAMA Neurol. 70 (3), 394–397.

Hoeltzenbein, M, Beck, E, Rajwanshi, R, 2016. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. Semin. Arthritis Rheum. 46 (2), 238–245.

Shosha, Eslam, Pittock, Sean J, Flanagan, Eoin, Weinshenker, Brian G, 2017. Neuromyelitis optica spectrum disorders and pregnancy: Interactions and management. Mult. Scler. 23 (14), 1808–1817.

Das, G, Damotte, V, Gelfand, JM, et al., 2018. Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. Neurol. Neuroimmunol. Neuroinflamm. 5, e453.

Chiesa, Claudio, Pacifico, Lucia, Natale, Fabio, 2015. Fetal and early neonatal interleukin-6 response. Cytokine 76, 1–12.

Huda, Saif, Whittam, Dan, Bhojak, Maneesh, 2019. Neuromyelitis optica spectrum disorders. Clin. Med. 19 (2), 169–176.