Should tocilizumab be the first line treatment for neuromyelitis optica together with rituximab?

¿Debería ser el tocilizumab el tratamiento de primera línea para la neuromielitis óptica junto con el rituximab?

Dear Editor,

Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated inflammatory disease of the central nervous system (CNS). The disorder affects the optic nerves, spinal cord and area postrema of the brain stem. 75% of patients diagnosed with NMOSD will have antibodies against the aquaporin 4 water channel (AQP4-abs) expressed on the astrocytes. Of the patients who do not have the AQP4-abs, 40% will have antibodies against the myelin oligodendrocyte glycoprotein (MOG-abs) present on the surface of oligodendrocytes which are the cells responsible in forming the CNS myelin. Around 50% of patients suffering from NMOSD will be wheel chair bound and blind within 5 years of their first attack if left untreated, and a third would have died.[1,2]

Plasmablasts (PB), which are a subpopulation of B cells, are increased in the peripheral blood of patients with NMOSD These B cells upregulate humoral immune response by producing antibodies and activating T cells by antigen presentation. Several studies have indicated a crucial role of B cells in the pathogenesis of NMOSD.[3,4]

Rituximab (RTX), a B-cell depleting monoclonal antibody, is being used as a first line treatment for NMOSD. RTX reduces relapse rates by up to 84.3% and is either given every 6 months or when the CD 19 counts of the total B-cell population rises above 1%.[3,5] On the other hand, patients who develop a longitudinally extensive transverse myelitis (LETM), which is the hallmark for NMOSD, have a 50% risk of a major spinal cord relapse within 12 months if they have the AQP4 abs and did not receive treatment, and a 15.6% relapse rate within 6 months after the induction dose of RTX. The relapse is usually devastating leaving permanent neurologic deficits and may well occur before the time of the second dose of RTX.[1,5]

Interleukin 6 (IL-6) is produced at the site of inflammation and plays a key role in the acute phase response. IL-6 in combination with its soluble receptor sIL-6Rα, dictates the transition from acute to chronic inflammation by changing the nature of leukocyte infiltrate (from polymorphonuclear neutrophils to monocyte/macrophages). In addition, IL-6 exerts stimulatory effects on T- and B-cells, thus favoring chronic inflammatory responses. Strategies targeting IL-6 and IL-6 signaling led to effective prevention and treatment of models of rheumatoid arthritis and other chronic inflammatory diseases. Studies have shown that IL-6 promotes the survival of PB and their production of AQP4-abs. Data suggests that the AQP4-abs induce IL-6 production in astrocytes expressing the AQP4, and that IL-6 signaling to endothelial cells reduces blood-brain barrier function. This results in further systemic AQP4-abs entering the CNS. Once bound to the AQP4 receptor on the astrocyte, the AQP4 abs result in complement and cell-mediated astrocytic damage. The damaged astrocytes will eventually withdraw support to the nearby oligodendrocyte. Granulocytes will invade further the region resulting in demyelination.[1,4]

Tocilizumab (TCZ) is an IL-6 receptor inhibitor. It binds soluble as well as membrane bound IL-6 receptors, hindering it from exerting its pro-inflammatory effects. TCZ treatment recently showed efficacy for patients with aggressive NMO who were refractory to the anti-CD20 antibody RTX.[4] The efficacy of TCZ could result from its effect on IL-6-dependent inflammatory processes, involving CD20-negative plasmablasts, pathogenic T cells, and regulatory T cells.[4] TCZ reduces the level of AQP4-abs in the serum and CSF of patients with NMOSD. It can reduce the frequency of attacks in NMO without concomitant immunosuppression, even in patients with high disease activity.[6,7]

Zhang et al. compared the efficacy of TCZ to azathioprine in the second line treatment of NMOSD. The incidence of serious adverse events was higher in the azathioprine group than the tocilizumab group. The most commonly reported adverse events were increased alanine transaminase concentrations, upper respiratory tract infections, and urinary tract infections.[8,9]

We suggest the use of TCZ, together with RTX, as a first line therapy for the treatment of NMOSD. This is important especially in patients with positive AQP4-abs and before relapses occur resulting in major disability. The combined therapy will not result in a critical immunosuppression and will have less side effect than the present combination treatments.

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Charcot-Marie-Tooth 4C and bilateral spinal dissection: causal or coincidental relationship?☆

Charcot-Marie-Tooth 4C y disección vertebral bilateral: ¿relación causal o coincidente?

Dear Editor:

Charcot-Marie-Tooth disease (CMT) is one of the most complex neurological syndromes, and presents a prevalence of 28.2 cases/100 000 population in Spain. CMT type 4C, which accounts for 18% of cases, is characterised by clinical symptoms of demyelinating neuropathy following an autosomal recessive inheritance pattern, and is more prevalent among people of Roma descent.[2,3,6,8] It is caused by a biallelic mutation of the *SH3TC2* gene, located on chromosome 5q32, which participates in encoding a membrane protein of Schwann cells, involved in endocytic recycling through the Rab11 GTPase system.[2—4,7,8] PCR and ELISA studies have detected the SH3TC2 protein in the tissues of the brain, spinal cord, cardiac muscle, testes, lungs, liver, skeletal muscle, kidneys, pancreas, ovaries, and spleen.[4,7] We describe the case of a patient with CMT type 4C and vertebral artery dissection.

The patient was a 37-year-old woman of Roma descent, born to consanguineous parents, who was under follow-up due to diagnosis of CMT type 4C (*SH3TC2* mutation p.R1109X in homozygosis). She visited the emergency department due to neck pain and sudden worsening of gait instability, a week after undergoing a cervical traction manoeuvre due to moderate cervical pain.

Neurological examination revealed severe dysarthria; persistent horizontal nystagmus in all gaze positions; right-sided trigeminal hypoaesthesia and facial palsy; deviation of the tongue to the right side; paresis and dysmetria of the right arm; and unstable, wide-based gait with a tendency to veer to the right. The patient scored 6 on the National Institutes of Health Stroke Scale. We initially suspected vertebrobasilar stroke presenting as right bulbo-pontine syndrome.

An emergency blood analysis (complete blood count, coagulation profile, electrolyte study, glycaemia, and kidney and liver function), ECG, and head CT identified no alterations. A CT angiography of the supra-aortic arteries (Fig. 1) identified reduced calibre of the right V2 and left V3 segments of the vertebral artery, without filling of the posterior inferior cerebellar artery (PICA), and a filling defect in the proximal third of the basilar artery, with distal filling; these findings are compatible with bilateral vertebral artery dissection and non-occlusive thrombosis of the proximal basilar artery.

We requested further testing, including a lipid profile, vitamins, thyroid function, total protein test, autoimmunity, and serology studies, as well as a transoesophageal echocardiography study and 24-hour Holter ECG monitoring; all studies yielded normal results. A follow-up head CT study performed at 24 hours identified subacute infarction in the territory of the right anterior-inferior cerebellar artery (AICA) and PICA, with no haemorrhagic transforma-

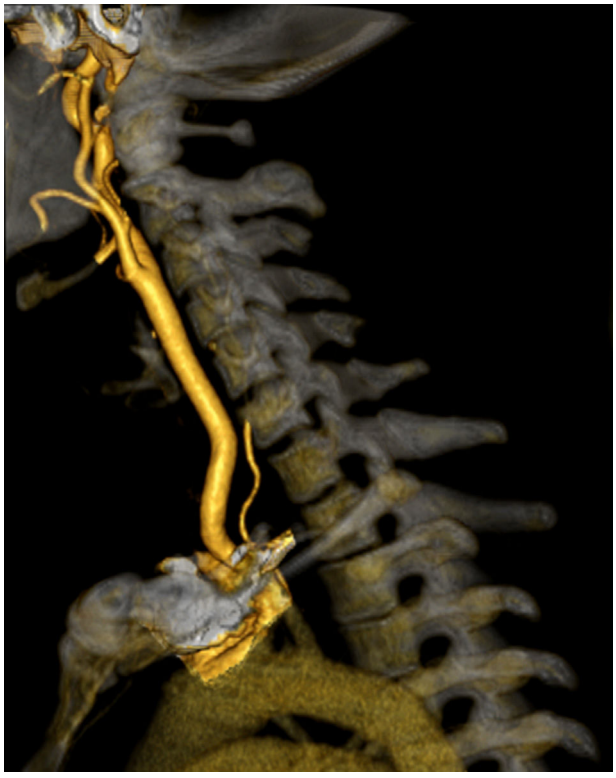

Figure 1 CT angiography reconstruction of the supra-aortic arteries: stenosis of the V2 segment of the left vertebral artery.

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