

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-6R α , 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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<https://doi.org/10.1016/j.nrl.2020.10.007>

0213-4853/

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

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

Sr. Editor:

La enfermedad de Charcot-Marie-Tooth (CMT) representa uno de los síndromes neurológicos más complejos, con una prevalencia de 28,2/100.000 habitantes en España. La variante 4C engloba un cuadro de neuropatía desmielinizante con herencia autosómica recesiva, constituyendo el 18% de los casos, con mayor prevalencia en etnia gitana^{2,3,6,8}. Es ocasionado por una mutación bialélica en el gen SH3TC2 (5q32) que participa en la codificación de una proteína situada en la membrana nuclear de la célula de Schwann, relacionada con procesos de reciclaje endocítico a través del sistema GTPasa Rab11^{2-4,7,8}. La proteína SH3TC2 ha sido identificada mediante PCR/ELISA en tejido encefálico, médula espinal, miocardio, testículo, pulmón, hígado, músculo esquelético, riñón, páncreas, ovario y bazo^{4,7}. Describimos un caso clínico con coexistencia entre CMT-4C y disección vertebral.

Mujer de 37 años, de etnia gitana y consanguinidad paterna, en seguimiento tras diagnóstico de CMT-4C (homocigosis para p.R1109X del gen SH3TC2), es valorada en el Servicio de Urgencias por cervicalgia y empeoramiento brusco en la inestabilidad de la marcha una semana después de recibir maniobra de tracción cervical por dolor cervical moderado.

A la exploración neurológica destaca disartria severa, nistagmo horizontal inagotable en todas las posiciones de la mirada, hipoestesia trigeminal y paresia facial derechas, desviación de la punta de la lengua a la derecha, paresia y dismetría en brazo derecho e inestabilidad de la marcha con aumento en base de sustentación y lateralización a la derecha, puntuando 6 en la *National Institute of Health Stroke Scale*. La sospecha clínica inicial fue de ictus vertebrobasilar cursando como síndrome bulbo-protuberancial derecho.

Inicialmente, se solicitaron analítica sanguínea urgente (hemograma, coagulación, ionograma, perfil glucémico, renal y hepático), ECG y tomografía computarizada craneal (TC), sin alteraciones. En angio-TC de arterias supraaórticas se objetivó una disminución de calibre en los segmentos vertebrales V3 derecho y V2 izquierdo sin relleno de PICA (arteria cerebelosa postero-inferior), así como un defecto de repleción en el tercio proximal de arteria basilar con

relleno distal, compatible todo ello con disección vertebral bilateral y trombosis basilar proximal no oclusiva (fig. 1).

Se completó el estudio analítico con perfil lipídico, vitamínico, tiroideo, proteinograma, autoinmunidad y serologías, además de ecocardiograma transesofágico y Holter-ECG 24h, sin alteraciones. El TC craneal de control a las 24h mostró un infarto subagudo en territorio de AICA (arteria cerebelosa antero-inferior) y PICA derechas sin transformación hemorrágica ni efecto masa. En resonancia magnética craneal (RM) y arteriografía cerebral, además de infarto en dos tiempos en territorio de AICA y PICA derechas afectando a los núcleos del V, VII y VIII par craneal (fig. 2) y trombosis mural en la arteria basilar proximal y segmentos V3-V4 derechos condicionando una estenosis del 50 y 75%, respectivamente, se confirma disección vertebral con irregularidades en la pared arterial compatibles con componente displásico en V2 izquierda.

La paciente presenta una evolución favorable, manteniendo hipoestesia y paresia facial derechas con dismetría en el brazo derecho, puntuando 1 en la *Escala Rankin*



Figura 1 Reconstrucción de angio-TC de arterias supraaórticas: estenosis vertebral en segmento V2 izquierdo.