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CASE REPORT

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Variable responses to rituximab treatment in neuromyelitis optica (Devic's disease)

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Abstract We have described two cases of Devic's disease patients treated with rituximab with different outcomes. The results indicate that there may be early unresponsiveness in very aggressive cases. Well designed clinical trials are needed to assess treatment effects in such a rare disease.

Key words Neuromyelitis optica • Devic's disease • Rituximab • Treatment

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Neuromyelitis optica (NMO) is a rare, severe and demyelinating disease that affects optic nerves and spinal cord and is characterised by a relapsing course and a rapid increase of disability [1, 2]. The presence of depositions of IgG and complement at regions of active myelin destruction, as well as the presence of NMO-IgG against aquaporin-4, supports a role for humoral immunity in its pathogenesis [3–5].

Immunomodulating and immunosuppressant therapies are widely used in such contexts, but so far no large trials have been conducted [6]. Recently, Cree and coworkers [7] have proposed the use of rituximab, a chimeric human-murine anti-CD20 monoclonal antibody, in severe NMO. Rituximab works by selectively depleting CD20+ cells (expressed by both pre-B-cells and mature B-cells) *in vivo* and has been shown to reduce the relapse rate in 8 NMO patients.

In order to provide new information to improve the understanding of this drug, we have described two new rituximab-treated NMO patients. Both cases fulfilled the diagnostic criteria proposed by Wingerchuk et al. [8], and anti-aquaporin-4 antibodies (Ab-AQP4) were found in both patients.

Case 1

A 30-year-old woman developed NMO in November 2005 after the recurrence of optic neuritis and transverse myelitis. Diagnosis was supported by the presence of granulocytic pleiocytosis in cerebrospinal fluid while oligoclonal IgG bands were not detected. Spinal magnetic resonance imaging (MRI) showed the presence of a cervical lesion more than 3 vertebral segments in length, T2-hyperintense and T1-hypointense with gadolinium-enhancement (Fig. 1). A brain MRI was negative for lesions at every time point in which it was performed. The serum tested positive for the presence of Ab-AQP4. Since the onset of the disease, the patient has experienced a very aggressive course of the disease with monthly spinal relapses, reaching an

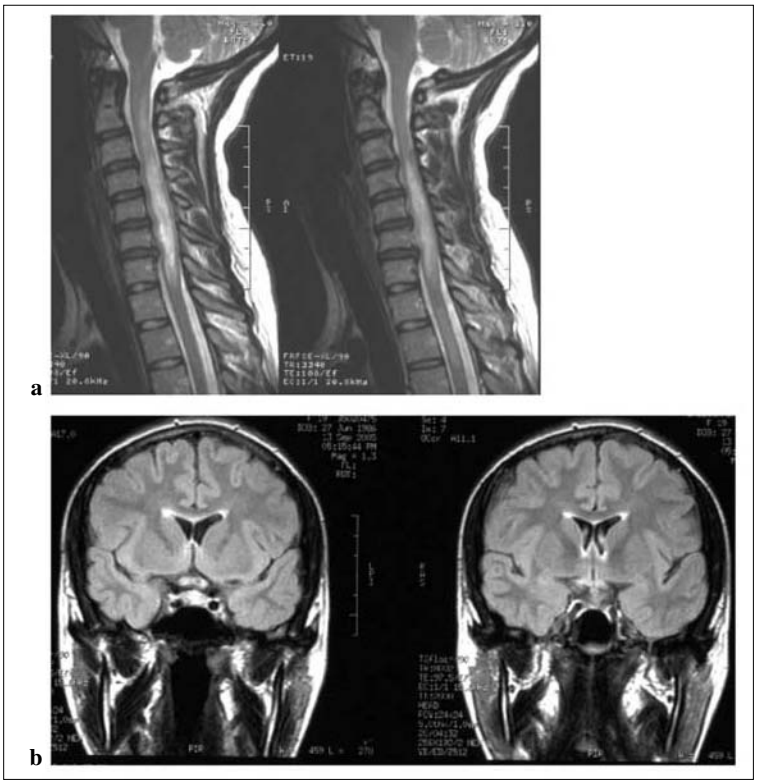

Fig. 1 MR imaging of the two Devic's disease patients. **a** Spinal MRI of case 1 showing extensive cervical T2-hyperintense lesion. **b** Brain and spinal MRI of case 2 showing bilateral optic nerves and chiasma involvement and extensive cervical T2-hyperintense lesion

Expanded Disability Status Scale (EDSS) score of 6.0 within 3 months. Although she had been consequently treated with intravenous high-dose methylprednisolone, plasma exchange (PLEX) and intravenous cyclophosphamide, she continued to experience new spinal relapses, reaching EDSS 7.5. After PLEX, she was treated with rituximab 375 mg/m^2 weekly for 4 weeks, lowering the EDSS score to 6.0. Although CD19+ cells (pre-B-cells) were still not detected, she experienced a new spinal cord relapse (EDSS 7.5) with a new concomitant spinal MRI enhancing-lesion, one month after the end of the treatment. She was promptly treated with PLEX, resulting in recovery to EDSS 6.0. Then she was treated with PLEX (3 procedures every other day) every three weeks, but after 4 months she experienced a new spinal relapse (EDSS 7.0) with the concomitant reappearance of CD19+ cells, and it was decided to treat her with two new infusions of rituximab, 1000 mg each dose, two weeks apart. At the last examination, after 2 months, she had improved to EDSS 6.5 and CD19+ cells were not detected (Fig. 2).

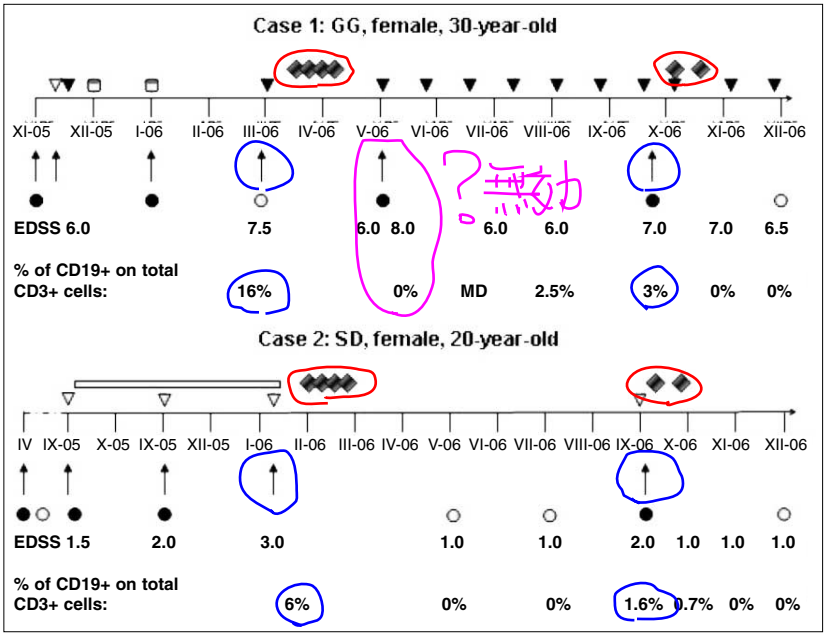

Fig. 2 Clinical courses of the 2 NMO Rituximab treated patients.
Roman numerals = months of the year; ◆ = rituximab pulse; ∇ = high dose intravenous corticosteroids; ↴ = plasmaexchange; ⊡ = cyclophosphamide pulse; ═ = interferon-beta 1a; EDSS = expanded disability status score; ↑ = clinical relapse; ● = spinal MRI showing no new and/or active lesions; ○ = spinal MRI showing new and/or active lesions. Relative quantification of CD19+ cells (normal value 5%–20%) is expressed as percentage of the total lymphocytes quantified by FACS analysis using antibodies anti-CD3

Case 2

A 20-year-old woman was diagnosed after experiencing bilateral optic neuritis and acute myelitis. Diagnosis was supported by the presence of bilateral optic involvement on brain MRI with no other brain lesions, a 3 vertebral segment wide T2-yperintense lesion on spinal MRI (Fig. 1) and the absence of oligoclonal bands in the cerebrospinal fluid. Serum Ab-AQP4 were detected. Earlier she had been treated with interferon-beta 1a (Rebif-44) with no response. The patient exhibited 2 subsequent spinal cord relapses two months apart, with EDSS progression to 3.0. After high-dose intravenous methylprednisolone, 375 mg/m^2 of rituximab was administered once a week for 4 weeks, with complete recovery. Bimonthly measurement of CD19+ cells showed B-cell depletion. Six months after the end of the treatment, she experienced a new mild spinal cord relapse (EDSS 2.0) also confirmed by the presence of a new MRI enhancing-lesion in the cervical spine. Concurrently, CD19+ cells were detected again and a new course of rituximab was performed after high-dose intravenous steroids had been administered. At the moment (6 months after the second course of rituximab) the patient is in a stable condition, scoring EDSS 1.0 and so far no new MRI lesions or activity have been detected. CD19+ cells still have not been detected (Fig. 2).

As far as we know this is the second report of NMO patients treated with rituximab.

These two cases describe different outcomes with Rituximab therapy and give key points to help in evaluating response to treatment and in understanding the pathogenetic mechanisms of NMO.

Very aggressive NMO, with early unresponsiveness to PLEX+Rituximab (case 1) has already been reported [9]. Several other antibodies that target antigens other than Aquaporin-4 were found in serum from this type of patient. Hence, it can be argued that different pathogenetic antigens are involved in NMO and that responsiveness to treatments depends on the different antigenic targets involved in the pathogenesis of the disease; it is possible that in the later phase of the disease, when high disability is reached, antigen spreading can appear, reducing the responsiveness to immunotherapy as observed in multiple sclerosis.

The proposed bimonthly interval detection of pre-B-cell during the follow-up [7] seems to be too long. Indeed, case 2 shows a clear correlation between the reappearance of CD19+ cells and disease activity. This case suggests that the evaluation of CD19+ cells should be performed at least every month, in order to restore B-cell depletion as soon as CD19+ cells are detected.

Rituximab should be recommended in aggressive Devic's disease. Nevertheless, other therapeutic options are possible: the use of mitoxantrone [10] has been proposed, but this drug seems to have a less favourable profile for the risk of developing myeloid leukaemia and dose-related cardiotoxicity. These risks seem to be higher than the reported cases of progressive multifocal leukoencephalopathy (PML) in systemic lupus erythematosus (SLE) patients treated with rituximab.

The use of rituximab for Devic's disease is off-label and this must be taken into account in the management of patients.

More data are needed to better define timing of infusion, timing of CD19+ cell count, beneficial effects rate and characteristics for responsiveness, and every effort must be made to conduct well designed trials on such a rare but highly disabling disease.

Sommario *Abbiamo descritto due casi di Malattia di Devic trattati con Rituximab con differente risposta terapeutica. I risultati indicano la possibilità di una non risposta precoce nei casi molto aggressivi. Sono necessari trial clinici ben strutturati per la valutazione dell'efficacia dei trattamenti in questa rara malattia.*

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