Getting to the root cause: the trouble with plasma cells

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Imagine: 15 years ago, a young woman is brought to your emergency room because of a series of seizures. She has a few days' history of amnesia, delusions and hallucinations. Diagnostic work-up reveals no focal neurological deficits, MRI is normal and CSF shows mild pleocytosis. An extensive search for infectious agents and systemic cancer proves negative. Over the next two weeks, the patient remains agitated and evolves to a coma with autonomic instability, continuous orofacial dyskinesias and limb choreoathetosis. No cause is identified. Perhaps the more fortunate patient receives a short course of high-dose steroids from a diagnostically-destitute clinician, or more likely no immunotherapies are commenced. Of course, nowadays, neurologists immediately consider requesting N-methyl-D-aspartate receptor (NMDAR)-antibodies. This syndrome was first described in 2007 as a paraneoplastic, ovarian teratoma-associated syndrome.[1] It was then reported in children, men and even elderly people,[2,3] surpassing the incidence of infectious agents in young people.[4]

NMDAR-antibodies principally bind the NR1-subunit of the NMDAR and induce internalization of these receptors.[5] This loss of surface NMDARs likely affects a variety of neurotransmitter systems, and overall excitability of neuronal networks. Around disease onset, serum levels of NMDAR-antibodies are approximately 10-fold higher than CSF levels, suggesting a peripheral immunisation. However, - CSF NMDAR-antibodies are always present in patients with the typical encephalitis,[3] and are detected at higher levels than would be expected for the total IgG.[2,6] This 'intrathecal synthesis' is likely secondary to antigen-specific antibody secreting cells (ASCs) found in the CSF, which

comprise about 10% of all CSF ASCs.[7] Thus, optimal therapeutic attempts should directly target the source of these causative antibodies: the ASCs found in the periphery, the CSF and, of course, the brain. Such therapeutic approaches may be pertinent to all antibody-mediated brain diseases.[6,8]

In these diseases, first-line treatments include corticosteroids, intravenous immunoglobulins and plasmapheresis, which result in improvement in ~50% of patients with NMDAR-antibody encephalitis. The remaining 'first-line-refractory' patients show objective improvements with the B-cell depleting agent rituximab (RTX) or the cytotoxic agent cyclophosphamide.[3] However, some patients respond poorly to these agents, and none of these medications are known to target the non-proliferative ASCs.

In this issue of *Neurology*, Scheibe et al. report five patients with treatment-refractory NMDAR-antibody encephalitis who were administered bortezomib (BTZ).[9] BTZ is a proteasome inhibitor, and the proteasome is a protein complex that clears proteins within cells. This function is especially critical for plasma cell survival due to their massive production of immunoglobulins. BTZ has proven efficacy in multiple myeloma and systemic lupus erythematosus.[10] Therefore, this therapeutic approach was both novel and biologically-plausible in patients with pathogenic NMDAR-antibodies.

The clinical and serological outcomes were promising. The authors concluded that BTZ reduces antibody titers and improves patients' clinical course. Interestingly, however, the effects on antibodies and clinical measures were not as marked as the biological

plausibility may have predicted. From the figure, Scheibe et al show that BTZ had a marked clinical effect in patients 1 and 3, and perhaps a less clear effect in patients 4 and 5. However, paradoxically, despite this modest clinical effect, CSF NMDAR-antibody titers only fell in two patients, including one measured over a two-year interval. In contrast, serum NMDAR-antibody levels fell more markedly and consistently.

The safety of subcutaneous BTZ was acceptable (no grade III or IV toxicities) in this population, although one patient developed fever and thrombocytopenia, and another was given antibiotics for an asymptomatic mycobacterium. The main established adverse effect of BTZ, polyneuropathy, spontaneously resolved in one patient.

The results of this study should be interpreted cautiously because of its retrospective design, the clinically-driven sampling timings, the small numbers, and the single center experience. The mixture of 'primary' and 'secondary' causes of NMDAR-antibody encephalitis adds to the heterogeneity. In addition, the multiple other immunotherapies are an inevitable confound. For example, rituximab induces a profound alteration in the cytokine profile, including some cytokines that are integral to plasma cell survival, such as IL-6. [11] Nevertheless, the authors' foray into the investigation of new therapeutics is commendable, the use of BTZ as an add-on medication is a sensible initial approach, and their results are broadly replicated by another report of two patients with the same condition. [12]

One critical question is whether the improvements observed with BTZ are consistent with the natural history of the condition. However, given the perceived observational evidence supporting immunotherapies, few examples of untreated patients might ever exist in the future. Nevertheless, one such early study showed near complete recovery in four patients – three with ovarian teratomas – over several years.[13] Of course, formal randomized studies are required to document unequivocal responses and our current reliance on observational data is dissatisfying.

Finally, another important question remains: does BTZ affect the brain? The limited reduction of CSF NMDAR-antibody titres in the face of serum depletions, suggests that BTZ has a dominant peripheral response. Indeed, BTZ does not cross the blood-brain-barrier and, based on the lack of MRI contrast enhancement, the blood-brain-barrier does not open substantially in NMDAR-antibody encephalitis. This raises intriguing questions about the mechanism of the clinical response, and biomarkers other than the antibodies themselves are required. Indeed, Scheibe et al's foray into novel immunotherapies might help future trials to evaluate clinical and biomarker-based outcomes, and to better understand whether earlier use of first and second-line treatment may abolish the need for BTZ, or whether earlier use of BTZ would benefit patients.

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