Of mice and people

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N2 often includes articles on mouse models and therefore the title of this Corner would be applicable to most N2 issues. Animal models represent the quintessence of translational research and are invaluable tools in neuroscience research. Modeling starts with a basic understanding of a human disease translated into a model that, if successful, will lead researchers back to the clinics armed with new theories and therapeutic possibilities. In the current issue of N2, there are several studies that exemplify the power of animal modeling to link the laboratory to the clinics.

Laquinimod is a quinolone-3-carboxamide that is being developed for the treatment of multiple sclerosis (MS), but its underlying therapeutic mechanisms are poorly understood. Studies have shown that laquinimod promotes development of type II myeloid antigen-presenting cells, which inhibit development of proinflammatory Th1 and Th17 cells.¹ Varrin-Doyer et al.² investigated whether laquinimod could also exert activity on several B-cell activities that contribute to CNS autoimmunity. These authors evaluated the effects of laquinimod on 2 experimental autoimmune encephalomyelitis (EAE) models that require B-T cell cooperation. In the recombinant myelin oligodendrocyte glycoprotein (MOG)-induced EAE model, they showed that laquinimod interfered with development of T follicular helper cells (T_{fh}, a CD4 T-cell subset that directs B-cell differentiation, germinal center formation, and immunoglobulin class switching), B-cell activation, secretion of MOG-specific antibodies, and EAE. In the spontaneous EAE model developed by crossing MOG-specific T-cell receptor transgenic mice (2D2) with MOG-specific B-cell receptor transgenic mice (Th), laquinimod reduced expansion of T_{fh} cells along with accumulation of meningeal B-cell aggregates, and inhibited disability progression when treatment was initiated after mice developed paralysis. Collectively, these findings may be relevant not only for the use of laquinimod in patients with progressive MS, but also for other antibody-associated disorders of the CNS such as neuromyelitis optica and anti-

NMDA receptor (NMDAR) and other autoimmune encephalitis.

Several studies on EAE have linked different immune mediators with preferential development of brain vs spinal inflammation.^{3,4} In a previous study, Stromnes et al.⁵ showed that parenchymal brain inflammation in EAE was enhanced when the ratio of Th17 cells to interferon (IFN)- γ -secreting T cells (Th1 cells) was ≥ 1 , whereas a ratio of Th17:Th1 ≤ 1 associated with inflammation largely restricted to the spinal cord. In the current study, investigators from the same group led by Johnson et al.⁶ analyzed the Th17 and Th1 ex vivo responses to 2 myelin proteins (myelin basic protein [MBP] and MOG) in peripheral blood mononuclear cells (PBMCs) of 3 human groups: patients with relapsing-remitting MS with predominant brain or spinal cord involvement and age-matched healthy controls. Interestingly, MBP and MOG elicited different responses; for MBP-specific responses, a major influence was the low IFN- γ response detected for spinal cord-predominant MS, whereas for MOG-specific responses, increased Th17 cells in spinal cord-predominant MS and increased Th1 cells in brain-predominant MS were the main factors in the Th17:Th1 ratios. An interesting question raised by the investigators is whether PBMCs are indicative of effector T-cell activity in the CNS, or if the peripheral T-cell responses reflect the inverse T-cell activity within the CNS because the CNS acts as a "sink" for pathogenic T cells. The latter would explain the opposite findings comparing the EAE model (where the Th17:Th1 ratio was examined in the CNS) with patients with MS where the T-cell ratios were examined in PBMCs. Future studies should clarify these questions, but results from this study suggest that the localization of lesions in the brain vs the spinal cord of patients with MS associates with different effector T-cell responses to myelin proteins, and possibly distinct pathogenic pathways depending on the area of the CNS that is predominantly affected.

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Identifying relapses vs pseudorelapses in neuromyelitis optica spectrum disorders (NMOSD) has important clinical implications for the type and duration of treatment and avoiding unnecessary immunotherapy and possible side effects. Kessler et al.⁷ examined early indicators of relapses vs pseudorelapses in 74 hospitalizations of patients with NMOSD. Relapses were defined as episodes of worsening symptoms and change in neurologic examination that correlated with new or enhancing MRI abnormalities; pseudorelapses were defined as exacerbation of symptoms but with negative MRI findings and identification of an alternative cause that when treated resulted in neurologic improvement. According to these criteria, 57 hospitalizations were due to confirmed relapses and 17 to pseudorelapses. Worsening visual acuity for more than 24 hours was strongly suggestive of a true relapse; in contrast, pseudorelapses localized to the spinal cord of patients with previous myelitis who otherwise presented as a true relapse but the MRI did not reveal new findings. Age at presentation, sex, race, urinary tract infection, leukocyte count, weakness, numbness, bowel/bladder symptoms, and aquaporin-4 antibody status were not significantly different between relapse and pseudorelapse cases. The authors acknowledged the limitations of the study, including the retrospective collection of data and the lack of inclusion of CSF pleocytosis in the definition of relapse.

Lejstue et al.⁸ examined the psychiatric manifestations of anti-NMDAR encephalitis in a retrospective review of 111 adults with this disorder. In 65 (59%), the initial symptoms were psychiatric, and 45 (40%) were first hospitalized in a psychiatric institution. Symptoms included hallucinations, depression, acute schizoaffective episodes, or mania, among others. In 87% of the patients, this was the first episode of psychiatric symptoms, but some patients had a history of psychiatric episodes that in retrospect were suspected to be anti-NMDAR encephalitis. The median duration of hospitalization in psychiatry units was 9 days (ranging from a few hours to 239 days). Interestingly, 24 of these 45 patients had neurologic signs at the first evaluation, but alternative diagnoses to a primarily psychiatric disorder were not considered. The reasons to transfer the patients from psychiatry to intensive care or other departments were the suspicion of neuroleptic malignant syndrome (NMS) in 47% of the patients, seizures (22%), other neurologic symptoms (e.g., amnesia, language dysfunction, 20%), and other reasons (e.g., EEG, MRI, family request, 11%). In the entire series, patients who received antipsychotics (typical or atypical) were more likely to develop fever than patients who did not. The authors emphasize the high rate of antipsychotic intolerance in patients with anti-NMDAR encephalitis, which in some clinical settings should lead practitioners to suspect this disorder.

Collectively, these findings and some interesting individual examples, such as the case of a patient treated for 1.5 years for schizophrenia who at examination showed pure retrograde amnesia suggesting alternative diagnoses (e.g., anti-NMDAR encephalitis), should lead to reflection and reconsideration of the criteria used for NMS and to a cautious use of the diagnosis of “schizophrenia” in patients harboring antibodies specific for NMDAR encephalitis.

Another interesting study by Zeydan et al.⁹ investigated the effectiveness of infliximab, a tumor necrosis factor- α blocker, for patients with neuro-Behçet syndrome refractory to other immunotherapies. The study included 16 patients with 2 or more neurologic relapses (excluding purely progressive disease). In one patient, infliximab was stopped due to pulmonary and CNS tuberculosis. In the other 15 patients, infliximab treatment abrogated the development of neurologic relapses with no further disability accumulation. These findings provide Class IV evidence that for patients with neuro-Behçet refractory to other immunotherapies, infliximab prevents relapses and stabilizes disability.

I hope this preview has piqued your interest to read these and the other equally interesting articles in this issue of N2.

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