Abstracts

Articles appearing in the January 2018 issue

Anti-LINGO-1 has no detectable immunomodulatory effects in preclinical and phase 1 studies

Objective To evaluate if anti-LINGO-1 antibody has immunomodulatory effects.

Methods Human peripheral blood mononuclear cells (hPBMCs), rat splenocytes, and rat CD4+ T cells were assessed to determine if LINGO-1 was expressed and inducible. Anti-LINGO-1 Li81 (0.1–30 µg/mL) effect on proliferation/cytokine production was assessed in purified rat CD4+ T cells and hPBMCs stimulated with antibodies to CD3+/-CD28. In humans, the effect of 2 opicinumab (anti-LINGO-1/BIIB033; 30, 60, 100 mg/kg) or placebo IV administrations was evaluated in RNA from blood and CSF samples taken before and after administration in phase 1 clinical trials; paired samples were assessed for differentially expressed genes by microarray. RNA from human CSF cell pellets was analyzed by quantitative real-time PCR for changes in transcripts representative of cell types, activation markers, and soluble proteins of the adaptive/innate immune systems. ELISA quantitated levels of CXCL13 protein in human CSF supernatants.

Results LINGO-1 is not expressed in hPBMCs, rat splenocytes, or rat CD4+ T cells; LINGO-1 blockade with Li81 did not affect T-cell proliferation or cytokine production from purified rat CD4+ T cells or hPBMCs. LINGO-1 blockade with opicinumab resulted in neither significant changes in immune system gene expression in blood and CSF or changes in CXCL13 CSF protein levels (clinical studies).

Conclusion These data support the hypothesis that LINGO-1 blockade does not affect immune function.

Classification of evidence This study provides Class II evidence that in patients with multiple sclerosis, opicinumab does not have immunomodulatory effects detected by changes in immune gene transcript expression.

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Fingolimod-associated PML with mild IRIS in MS: A clinicopathologic study

Objective To clarify the clinical, neuropathologic, and virologic characteristics of progressive multifocal leukoencephalopathy (PML) and its immune reconstitution inflammatory syndrome (IRIS) in a fingolimod-treated patient with multiple sclerosis (MS).

Methods Case study.

Results A 34-year-old patient with MS using fingolimod for 4 years had gradual progression of right hemiparesis and aphasia with a new subcortical white matter lesion in the precentral gyrus by initial MRI. Blood tests were normal except for lymphopenia (160 cells/µL). One month after the cessation of fingolimod, brain MRI depicted a diffusely exacerbated hyperintensity on fluid-attenuated inversion recovery and diffusion-weighted imaging in the white matter with punctate gadolinium enhancement, suggesting PML-IRIS. A very low level of JCV DNA (15 copies/mL) was detected in CSF as judged by quantitative PCR. Brain tissues were biopsied from the left frontal lesion, which showed some small demyelinated foci with predominant loss of myelin-associated glycoprotein with infiltrations of lymphocytes and macrophages, but clear viral inclusion was not observed with hematoxylin & eosin staining. JCV DNA was uniquely detectable in an active inflammatory demyelinating lesion by in situ hybridization, possibly suggesting early phase of PML. DNA extracted from brain sample was positive for JCV DNA (151 copies/cell). It took 3 months to normalize blood lymphocyte count. The patient was treated with 1 g of IV methylprednisolone for 3 days and a weekly oral dose (375 mg) of mefloquine, and her symptoms gradually improved.

Conclusion Low CSF JCV-DNA and unfound viral inclusions initially made diagnosis difficult. The clinical course of fingolimod-associated PML may be associated with mild immune reconstitution.

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