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Strategies to overcome intrathecal inflammation in progressive multiple sclerosis

Bibi Bielekova

MD, Mika Komori, MD/PhD, Simone Wuest, PhD and Peter Kosa, PhD NIH/NINDS, USA

Because of inadequate efficacy of immunomodulatory treatments, primary- (PPMS) and secondary-progressive multiple sclerosis (SPMS) were thought to have significantly less intrathecal inflammation than relapsing-remitting (RRMS) MS. Using functional assays and innovative combinatorial cerebrospinal fluid (CSF) biomarkers, we demonstrated that both progressive MS subgroups have on average identical amount of intrathecal inflammation to RRMS. Instead, significantly greater level of compartmentalization of immune responses to central nervous system (CNS) tissue and greater terminal differentiation of intrathecal immune responses were characteristic of progressive MS. This makes progressive MS inflammation inaccessible to systemically-administered large molecules (e.g. monoclonal antibodies; mAb), while small molecules that may penetrate CNS are ineffective, because they predominantly target cells in proliferation cycle. Thus, in the placebo-controlled, Phase II clinical trial (RIVITALISE trial, clinicaltrials.gov identifier NCT01212094) we investigated whether intrathecal (IT) administration of mAb, such as rituximab can effectively inhibit intrathecal inflammation in SPMS. The trial was stopped for futility, after prospectively-acquired CSF biomarkers convincingly demonstrated that IT-administered rituximab decreased intrathecal inflammation only by approximately 10%. Mechanistic studies revealed following reasons for decreased efficacy of rituximab in the intrathecal, as compared to systemic compartments: 1. Due to active transport of antibodies from CSF to blood, achievable CSF concentrations of rituximab did not fully saturate CD20 on intrathecal B cells. 2. CSF lacks lytic complement, which results in decreased complement-dependent cytotoxicity (CDC). 3. The predominant cellular subtype of natural killer (NK) cells in CSF are CD56bright NK cells, which have low expression of Fc receptor and thus decreased levels of antibody-dependent cellular cytotoxicity (ADCC).

In conclusion, novel immunomodulatory agents with high CNS penetrance, not dependent on CDC or ADCC and effective on proliferation-quiescent immune cells will be necessary to successfully inhibit intrathecal inflammation in progressive MS.

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Biography

Bielekova received an M.D. degree in 1993 from Comenius University in Bratislava, Slovakia. After a medical internship at SUNY Downstate, Medical Center in Brooklyn and a neurology residency at Boston University, she did a 3 year postdoctoral research fellowship at the NIH/NINDS/Neuroimmunology Branch (NIB). She remained at NIB for additional 5 years as a staff physician, focusing on development of novel therapies for multiple sclerosis (MS). In 2005, she became associate professor of neurology with tenure and director of the Waddell Center for MS at University of Cincinnati. In 2008, she moved back to NINDS as an investigator. Her laboratory is studying mechanisms of immunoregulation and immune-mediated central nervous system (CNS) tissue injury in MS and other neuroimmunological diseases with a long-term goal of developing effective therapies. In addition, Dr. Bielekova is a principal investigator on several innovative protocols including adaptively-designed Phase I/II clinical trials.

Bibi.Bielekova@nih.gov