Neurology/Psychiatric

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Nasal anti-CD3 antibody improves Alzheimer's disease in mice

By Mar de Miguel (/authors/595-mar-de-miguel)

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Alzheimer's disease (AD) has a new candidate for its treatment. Nasal anti-CD3 monoclonal antibody (MAb) reduced microglia activation in the brain of mice without its effect being dependent on the β-amyloid (Aβ) deposits characteristic of this neurodegenerative disorder.

"We have done many basic studies in the laboratory on microglia. Microglia activation occurs in many neurologic diseases. One of them is multiple sclerosis (MS). And it also occurs in AD," senior author Howard Weiner told *BioWorld*.

His goal was to find out whether they could dampen or modulate microglial activation. They first tested the anti-CD3 in animal models of MS. "Now we are treating MS patients and we are getting positive results," he said.

Weiner, a professor of neurology at the Harvard Medical School, is the director and founder of the Brigham Multiple Sclerosis Center, co-director of the Center for Neurologic Diseases and a principal investigator at The Gene Lay Institute of Immunology and Inflammation at the Brigham and Women's Hospital. There, he studied AD and also found microglial activation.

AD is characterized by the deposition of Aβ plaques and neurofibrillary tangles of phosphorylated tau protein in the brain that lead to neuroinflammation and a neurotoxic effect that causes the death of neurons and leads to cognitive impairment. The fact that Aβ plaques are surrounded by astrocytes and activated microglial cells suggests an inflammatory role in the development of the disease.

In a previous study (https://doi.org/10.1002/alz.068761), Weiner and his colleagues treated a mouse model of AD with a nasal anti-CD3 MAb for up to 6 months to examine cognitive behavior, microglia gene expression and T-cell infiltration in the brain.

Cluster of differentiation 3 (CD3) is a protein complex, a co-receptor involved in activating cytotoxic T cells and T helper cells. Intravenous CD3 MAbs are immunosuppressive drugs designed for the treatment of autoimmune and inflammatory diseases. Nasal anti-CD3 induces an effective tolerogenic response through its interaction with the mucosal immune system, which improves its safety.

In AD mice, microglia lose their functional phenotype, the homeostatic signature M0, and acquire a disease-associated phenotype, the neurodegenerative signature MGnD, which drives neuroinflammation. However, the treatment with nasal anti-CD3 MAb increased the expression of *Cx3cr1, Mafb* and *Jun*. This restored the M0 signature. Furthermore, the expression of *Trem2, Nos2* and *Ccl5* was decreased, which reduced the MGnD signature.

The scientists also observed an increase of the migration of T cells to the brain and demonstrated improved cognition in the treated animals. Their results suggested that the nasal anti-CD3 MAb modulated microglial neuroinflammation.

These results add to previous studies with the nasal anti-CD3 MAb in murine models of progressive MS, diabetes, arthritis and lupus. In patients with progressive MS and mild COVID-19, nasal foralumab, an anti-CD3 MAb from Tiziana Life Sciences Ltd., reduced microglial and lung inflammation, respectively.

Now, in this study (https://doi.org/10.1073/pnas.2309221120) published on September 4, 2023, in the *Proceedings of the National Academy of Sciences (PNAS)*, Weiner's laboratory went one step further and demonstrated that the activation of microglia in the brain is independent of the deposition of Aβ. This step helped identify the anti-CD3 effect, as Aβ deposits activate microglia.

The scientists observed that anti-CD3 treatment in AD mice reduced microglial activation and improved cognition. They associated this improvement with the infiltration of T cells in the brain in close contact with microglial cells. Furthermore, they demonstrated that the treatment reduced oxidative stress, increased the development of nerve axons and synaptic organization, and modified the metabolism of the cortex and the hippocampus.

"We are showing that the nasal anti-CD3 works," he said. This basic study showed that nasal anti-CD3 modulated microglial activation in animals before trying it in affected people.

His results propose a new immunotherapy approach to treat AD that could be combined with anti-amyloid therapy.

His laboratory is already studying the effect of nasal anti-CD3 combined with other treatments for AD in animal models. However, the first clinical trials will be separate. "Together with Tiziana Life Sciences, we will measure the effects of nasal foralumab on cognition and microglial activation in people. Once we establish that it works, then it could be given with other therapies," he said.

As for his next studies, Weiner said, "The next step in Alzheimer's is to show an effect in early Alzheimer's and then test a larger number of patients, and maybe patients with later-stage disease," he said.

Regarding effects in later stages of AD, Weiner's expectations are based on the independent effect of anti-CD3 of deposition of Aβ protein. "The anti-amyloid therapy only works early because amyloid comes first. I think that the microglia activation could be important in later stages when anti-amyloid therapy does not work. The microglial activation could be affecting cognition and thus we might see improvement in cognition when we treat later-stage people," he explained.

The scientist wonders how well the treatment will ultimately work in people and whether it works in other neurologic diseases where there is microglia activation, like traumatic brain injury, amyotrophic lateral sclerosis (ALS) and Parkinson's disease. "We have a grant to study it in ALS," he said (Lopes, J.R. et al. Proc Natl Acad Sci U S A 2023, 120(37): e2309221120).