Can a vaccine prevent Alzheimer's disease?

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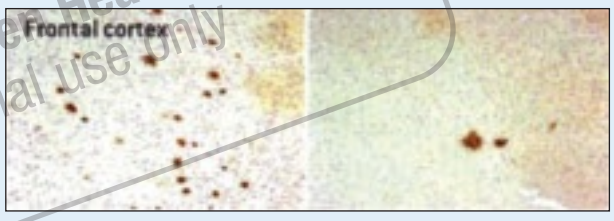
Figure 1
Differences in amyloid deposition between control and immunized mice



Frontal cortex of an unvaccinated mouse (left) shows more amyloid deposits (dark spots) than that of a mouse producing antibodies against the amyloid-β peptide (right).
Source: Image by Cynthia A. Lemere, PhD. Used with permission.

Deposition of amyloid-β peptide (Aβ) is believed to contribute to Alzheimer's disease (AD) pathogenesis. Derived from a larger precursor protein, Aβ aggregates into plaques, and may promote neuronal death and, ultimately, dementia.

Current treatments alleviate symptoms without slowing underlying neurodegeneration. The prospect of harnessing the immune system to target the Aβ peptide offers an intriguing option for preventing this devastating, increasingly common disease.

ANTI-Aβ ANTIBODIES

Transgenic mice bred to overexpress AD genes have responded remarkably in studies using the immune system to target the amyloid-β peptide.[3] Several mouse groups have shown plaque reduction (*Figure 1*) and improved cognitive performance. These findings substantiate the amyloid hypothesis in AD pathogenesis.

A host could acquire anti-Aβ antibodies though two basic approaches (*Figure 2, page 30*):[2]

Active immunization exposes the subject to the antigen (in this case the Aβ peptide) and allows T cells and B cells to produce anti-Aβ antibodies. This approach has been studied in humans, but adverse effects have stymied its development.

Passive immunization, which involves developing anti-Aβ antibodies in a separate source, aims to clear Aβ peptide without requiring an immunologic response from the host. Large doses of antibodies administered weekly or monthly would be needed to build adequate plasma levels in the CNS, and large quantities of circulating antibodies could cause hemorrhagic stroke.

A TROUBLESOME TRIAL

After successful preclinical and phase 1 testing of a vaccine against the Aβ peptide (called AN-1792), a phase 2a placebo-controlled trial in 2001 followed patients with mild to moderate AD. Drug administration was halted after 18 patients (6%) developed meningoencephalitis after several months.[4] However, 300 patients with AD and 72 control patients had

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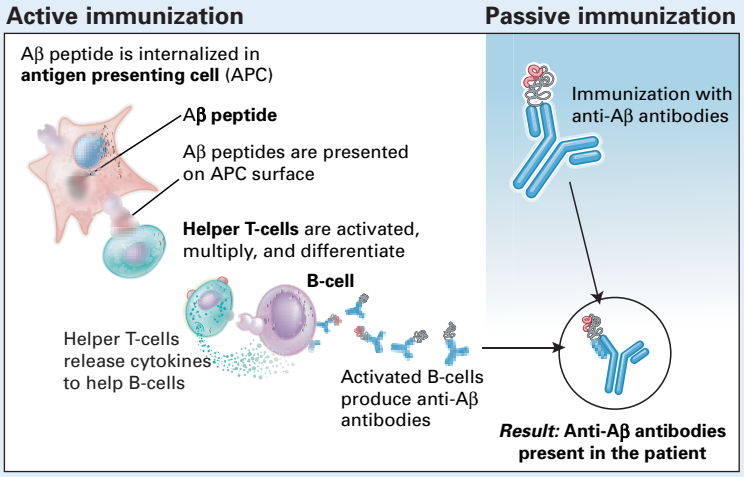
Figure 2

Methods for immunizing against Aβ peptide



Active immunization produces anti-Aβ antibodies via immunologic response to vaccination. With passive immunization, anti-Aβ antibodies are administered directly.

Illustration by Rich LaRocco.

received at least one injection, and double-blind assessments were maintained for 12 months.

All patients with meningoencephalitis had received the vaccine but not all developed an immune response, suggesting that something other than the antibodies—such as T cells—caused the encephalitis. Twelve patients recovered, but six had persistent cognitive and neurologic deficits.

MORE-OPTIMISTIC NEWS

Of the 300 patients who received an active vaccine, 20% developed an adequate antibody response.[5]

The responders showed no significant difference from the placebo group in most outcome measures but showed less worsening in the nine-component Neuropsychological Test Battery (NTB) ($P = 0.02$). Of particular interest, antibody responders showed significant improvement in the NTB's memory domain ($P = 0.03$). Further, subjects with higher IgG antibody titers showed greater improvement than did other responders.

MORE WORK AHEAD

Although the outcome of this initial AN-1792 trial is disappointing because of its discontinuation and mixed results, T cell infiltration and amyloid depletion were found during postmortem examinations of two vaccine recipients.[6]

Pharmaceutical companies are testing two compounds for AD immunotherapy:[7]

- AAB-001, a human monoclonal antibody, targets all 42 Aβ amino acids via passive immunization and has entered phase 2 trials.
- ACC-001, an Aβ immuno-conjugate designed to elicit an active antibody response, began phase 1 testing last fall.

These efforts suggest that an "Alzheimer's vaccine" could be produced, provided it could attack the Aβ peptide without inducing a significant cellular reaction.

References

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