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Alzheimer's vaccine: a cure as dangerous as the disease?

Rapid Communication

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Summary. Studies in transgenic mouse models of Alzheimer's disease suggested the potential for a vaccine development. However, some patients in the human clinical trials developed symptoms of brain inflammation, demonstrating the high risk of a deliberately induced auto-immune response.

Keywords: Alzheimer's disease, vaccine, inflammation, auto-immune disease

Prospects for a safe vaccine to treat Alzheimer's disease received a setback when Elan Corporation and Wyeth-Ayerst Laboratories temporarily suspended their phase 2A clinical trials of AN-1792 in January after some patients developed unwanted side effects. In France, 4 of 97 subjects reportedly developed symptoms of central nervous system inflammation (Check, 2002). In the meantime, similar incidents of meningoencephalitis were reported from other study centers; the number of affected patients has risen to 15 among the 360 patients participating in the clinical trials worldwide (Weiss, 2002). Details of their symptoms have not been released but inflammatory conditions of the nervous system such as meningitis and assumed multiple sclerosis are debilitating and can be fatal.

AN-1792 targets amyloid-beta (Aβ), the principal constituent of senile plaques. It is thought that brain damage in Alzheimer's disease is caused when these plaques deposit in the cerebral cortex. Transgenic mice can be engineered to develop plaques and Elan's researchers demonstrated that vaccination with Aβ clears their plaques and improves their memory (Arendash et al., 2001; Schenk et al., 1999). Vaccination with Aβ stimulates the production of specific antibodies that facilitate its removal from plaques by cells of the immune system (Bard et al., 2000). In effect, it produces an autoimmune

response against a naturally occurring protein sequence in the brain. If the cases of nervous system inflammation in the AN-1792 trials are due to an autoimmune response, their treatment will be problematic. The condition is likely to be irreversible and will have to be controlled by immunosuppressive drugs, if the immune reaction overshoots. Such treatments in the elderly are contra-indicated due to the high risk of contracting secondary infections and other complications. Also of concern is the possibility that other patients in these trials who initially have a lower titre of antibodies will develop the same symptoms over a longer period of time.

One might hope that the inflammatory condition afflicting patients in the AN-1792 trials may turn out to be unrelated to their vaccination, and the high frequency of serious side-effects may be an anomaly produced by clustering within a small sample. However, some researchers have warned that vaccination with Aβ risks producing serious side-effects including the activation of amyloid specific cytotoxic T-cells (Grubeck-Loebenstein et al., 2000). Moreover, the antibodies may also target the amyloid precursor protein, which is present on neurons and assists the protection and repair of brain cells. Its recognition by antibodies and subsequent opsonisation could cause widespread brain damage. Furthermore, cytokines produced by activated cells of the immune system can stimulate the synthesis of Aβ. In other words, vaccination with Aβ may promote its production and complete a vicious cycle of neuroinflammation and brain injury.

Symptoms of brain inflammation have not been reported in transgenic mice vaccinated with Aβ. These mice are genetically engineered to express human amyloid precursor protein in a subset of brain cells, and are then vaccinated with human Aβ (Arendash et al., 2001; Schenk et al., 1999). Since the human form of this peptide is structurally different from the mouse form, the mouse probably makes antibodies that only recognise the human Aβ. These antibodies would target the few cells that produce human Aβ while leaving most brain cells intact. To properly mimic the immune response induced in the human trials, normal wild-type mice would have to be vaccinated with the mouse form of Aβ. There is an urgent need to examine such mice for signs of neuroinflammation before continuing or expanding the human trials. These experiments may assist the development of ways to reduce the unwanted side-effects, or at least help us to understand whether it is possible to safely induce an autoimmune response in order to treat Alzheimer's disease.

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