Future Therapeutic Approaches to Alzheimer's Disease

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As palliative treatments for Alzheimer's disease proliferate, the focus of therapeutics turns to drugs with the potential to alter course. Evidence is reviewed, suggesting that there is biological plausibility to utilizing anti-inflammatory agents, antioxidants, free-radical scavengers, estrogen preparations, and perhaps cholinomimetics. This range of possibilities leads to an optimistic assessment of the likelihood for altering the course or delaying the onset of Alzheimer's disease. *(J Clin Psychiatry 1998;59[suppl 11]:14–16)*

Experimental therapeutic approaches to Alzheimer's disease are centered on the question of whether the course of Alzheimer's disease can be altered. To do so would have enormous epidemiologic, social, and economic consequences. Given the very late-life incidence of Alzheimer's disease, a few years' delay in onset would substantially decrease its prevalence.

This paper addresses three areas: the possibility that drugs that have already been approved, such as the cholinesterase inhibitor tacrine, and others that are nearing approval may alter the course of Alzheimer's disease; whether drugs that are available but not approved for Alzheimer's disease (so-called off-label indications), such as anti-inflammatory agents, may slow the course of Alzheimer's disease; and if molecular approaches can block the β-amyloid receptor, assuming such a receptor exists.

CHOLINESTERASE INHIBITORS

Cholinesterase inhibitors have palliative effects on the symptoms of Alzheimer's disease.[1–3] Tacrine is currently approved for use in Alzheimer's disease, and E2020 is likely to be available shortly. A host of other, "second generation" cholinesterase inhibitors, such as metrifonate, ENA (Exelon), galantamine, and oral physostigmine, are in pivotal trials. Thus, it is likely that in the near future the practitioner will have a host of cholinesterase inhibitors from which to choose. Furthermore, this armamentarium might be further augmented with the addition of M_1 agonists, such as SB202026 and xenomeline.[4] The agent likely to be most widely used will be the one with a duration of action that requires minimal dosing (but that does not accumulate), few drug interactions, low plasma-protein binding, and the most favorable adverse event profile. It is likely that if any one compound should possess these characteristics, the entire class of compounds will probably do so as well. Indeed, that very possibility has been raised by recent data obtained with tacrine.

In one of the pivotal tacrine studies, patients received 80 mg, 120 mg, or 160 mg of the drug.[2] When the study was completed, many patients continued to take tacrine. These patients were evaluated in follow-up data analysis. Those who received less than 80 mg of tacrine had a more than 50% probability of entering a long-term care facility. The patients who received more than 80 mg (120 mg or 160 mg) of tacrine for 2 years or more had a likelihood of entering a long-term care facility of only 25%. Despite these provocative results, this analysis was deficient in that it was retrospective, did not include a control group, and had selection biases inherent in patients who tolerated a higher dose of tacrine.

Interestingly, data support a biological plausibility that cholinergic compounds alter the course of Alzheimer's disease.[5–9] The amyloid precursor protein (APP) molecule includes β-amyloid, a 42-amino acid peptide that comes from a larger molecule. Depending on where there is cleavage in the molecule, β-amyloid can form into plaques. In a recent study,[10] APP was measured in two groups of rats: one group received a nucleus basalis lesion, and the other group had a sham operation. The lesioned animals produced more APP than the sham controls. APP was elevated as measured by both protein and messenger RNA (mRNA). Soluble forms of β-amyloid, measured by specific antibody to the β-amyloid-containing portion of APP fragments, was also significantly increased. Similar results were obtained when lesions were placed in the dorsal raphe, as well as when neurotransmission was simply diminished by the injection of lidocaine. The degree to which cholinergic activity was decreased in these animals correlated robustly with the degree to which there was an increase in β-amyloid-related fragments in the ventricular fluid.

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Superimposed on this model system was the administration of a series of cholinesterase inhibitors. Some, but not all, cholinergic manipulation decreased β-amyloid levels. For example, phenserine, but not diisofluorophosphate, diminished soluble β-amyloid immunoreactivity in the ventricular fluid of these lesioned rats.[11,12] This is consistent with the notion that a cholinesterase inhibitor might be able to alter the course of Alzheimer's disease if administered over a long enough period of time and could be a biological basis for the observations made in the long-term care study.[2]

ANTI-INFLAMMATORY AGENTS

Anti-inflammatory agents are not approved for altering the course of Alzheimer's disease. Inflammatory mechanisms in the Alzheimer brain are reflected in a host of changes.[13] There is an activation of the complement cascade and increased levels of microglia. There are elevations in cytokines, interleukin-1 and -6, and the acute-phase proteins accompanied by increases in α_1-antichymotrypsin, α_2-macroglobulin, C-reactive protein,[14] and plasma.[15,16] In a recent study, the Alzheimer group had almost twice the level of α_1-antichymotrypsin in their plasma than age-matched normals, and the first-degree relatives of the Alzheimer group had intermediate α_1-antichymotrypsin levels (reference 17 and Gabriel SM, Marin DB, Aisen PS, et al. Manuscript submitted). It is known that many first-degree relatives of Alzheimer patients are at high risk for the disease.[18]

There is a relationship between cognition and the severity of the acute-phase response in patients with Alzheimer's disease, the lowest Mini-Mental State Examination score, and the lowest acute-phase response as reflected in C-reactive protein, α_2-macroglobulin, or α_1-antichymotrypsin. This relationship suggests that the acute-phase response occurs early and robustly in Alzheimer's disease, and decreases as the disease progresses. This has obvious implications for the acute-phase response, which is an early, even premorbid, marker of Alzheimer's disease.

A number of cytokines are elevated in the Alzheimer brain. Interestingly, cytokines can induce the enhanced transcription of APP.[19] A further link between interleukins and Alzheimer's disease derives from data obtained from cholinergic cultured neurons. Apparently, the toxicity of β-amyloid in culture is enhanced by the presence of interleukin-1.[20] Thus, some components of the inflammatory reaction of the Alzheimer brain may contribute to further neuronal loss. This possibility is enhanced by observations concerning the activation of complement in the Alzheimer brain.[21] The whole cascade, including the membrane-attack complex, appears to be present in Alzheimer's disease. β-amyloid binds to the initiating protein in the complement cascade to begin this potentially destructive process.[22]

What part of the inflammatory reaction should be a target for Alzheimer's disease therapeutics, that when blocked would facilitate the preservation of neurons at risk in Alzheimer's disease? Since so many components of the inflammatory reaction in the brain are connected, targeting any one component is difficult. It is hard to know where to intervene and what drug to choose.

Corticosteroids such as prednisone are the most effective and broad-spectrum agents in inhibiting a CNS-inflammatory response. Because nonsteroidal anti-inflammatories such as ibuprofen have been shown by epidemiologic studies to perhaps delay the onset of Alzheimer's disease,[23,24] they therefore make interesting candidates. These epidemiologic data, however, are somewhat surprising because nonsteroidal anti-inflammatory agents such as indomethacin are prostaglandin inhibitors and diminish neutrophil activation. With the many inflammatory components in the Alzheimer brain, prime targets to decrease would not be prostaglandins and neutrophil activation. Nonetheless, the epidemiologic studies are compelling. Other drugs worth investigating are antimalarials, colchicine, and dapsone. In cell culture, when an anti-inflammatory such as indomethacin, dexamethasone, or chloroquine is added to β-amyloid, the survival of cells is enhanced.[20]

We have chosen to study the effects of prednisone on Alzheimer's disease because it is the broadest anti-inflammatory; has widespread efficacy in other CNS rheumatic-type diseases, including cerebritis and vasculitis; and can suppress the acute-phase response and complement activation. We first conducted a pilot study to see if, and at what dose, the key biological measures of the inflammatory response would be suppressed.[25,26] When 20 mg of prednisone was administered for 2 weeks, stepped down for 1 week to 10 mg, and then ultimately tapered to discontinuation by 8 weeks, the following result occurred: prednisone effected diminution of α_1-antichymotrypsin, which remained low even when the dose was discontinued. C-reactive protein levels were reduced and stayed low through the 10-mg dose, but returned to baseline levels at the end of the trial when the drug was discontinued. The complement split product was reduced by prednisone as well. A lower dose of prednisone did not suppress the acute-phase response as reflected in plasma levels of α_1-antichymotrypsin.

As a consequence of the pilot study results, a double-blind placebo-controlled study is now ongoing. Patients will receive prednisone or placebo for a year. There are 22 sites, with an intended enrollment of 150 subjects. So far, 120 subjects have been enrolled, and there have been no toxic or serious adverse events and no dropout due to toxicity.

MOLECULAR APPROACH

The search for the β-amyloid receptor has been challenging for many pharmaceutical companies involved in Alzheimer's disease research. If there really is a receptor for

β-amyloid, then a drug might be developed to block β-amyloid neurotoxicity. Toward this end, the frog oocyte expression system has been utilized. Frog oocytes are large cells that are genetic machines. If these cells are injected with mRNA, they produce proteins for those messages. A library of mRNA was injected into the oocytes to determine if they would respond to β-amyloid. When a message is injected and a receptor synthesized, the receptor will eventually migrate to the external surface of the oocyte. If β-amyloid is applied to the cell and a β-amyloid receptor exists, there may be a response. Should the receptor be mediated by a G protein–coupled receptor, changes in inositol phosphate, and ultimately changes in calcium and chloride fluxes across the oocyte, should be detectable by an electrode placed in the cell. The results of numerous oocyte injections and measurements after whole brain message injections was that nanomolar concentrations of β-amyloid produced changes in electrical activity. Those findings were replicated in 20 experiments in which low concentrations of β-amyloid stimulated the oocyte.

Thus, β-amyloid in low concentrations can produce a substantial increase in electrical current that could occur only if there was a β-amyloid receptor that the oocyte manufactured in response to the injection of the right mRNA. Since the mRNA came from brain preparations, these results suggest that there may be a specific β-amyloid receptor that can be expressed in the oocyte system. As a consequence, those receptors could be cloned to develop drugs that can block that receptor or produce agonist effects at its site. The therapeutic implications of drugs that work specifically at a putative β-amyloid receptor would be enormous.

CONCLUSION

In summary, when cholinesterase inhibitors were first administered to Alzheimer patients in 1979, one could hardly conceive that this would eventually lead to a group of compounds with a palliative effect to reduce symptoms in patients with Alzheimer's disease. In a little more than 10 years, this effect has become reality. In another 10 years, we should see drugs that alter the course of Alzheimer's disease. Thus, in our generation, we will have substantially altered what is perhaps the most feared late-life disease.

Drug names: chloroquine (Aralen), dexamethasone (Decadron and others), ibuprofen (Advil and others), indomethacin (Indocin and others), lidocaine (Xylocaine and others), prednisone (Deltasone and others), tacrine (Cognex).

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