Neuroprotection: promise and pitfalls in anti-inflammatory treatment of Alzheimer's disease

At present, more than 20 observational studies show an inverse association between NSAID use and Alzheimer's disease. A landmark prospective epidemiological study published in the *New England Journal of Medicine* last November reported that non-steroidal anti-inflammatory drugs (NSAIDs) significantly decrease the risk of Alzheimer's disease (AD), especially if taken for periods of two years or more. This is one of the most recent epidemiological studies to suggest that NSAIDs protect against AD and may, therefore, have therapeutic potential. However, several recent studies have failed to show a therapeutic effect of NSAIDs in AD. Clinicians and scientists currently believe that the lack of efficacy of NSAIDs is attributable to two key problems. First, previous clinical trials of NSAIDs included patients with advanced AD, in whom neurodegenerative changes (including neuronal loss, amyloid plaques, and neurofibrillary tangles) were already rampant. Also, given that epidemiological data are based on NSAID use before the onset of AD (prophylactic), clinical trials may be more successful if performed in the early or preclinical stages of the disease. Second, it is currently not known which NSAIDs (e.g., cyclooxygenase [COX]-1 or COX-2 inhibitors) will prove to be most effective in preventing or treating AD.

Accordingly, a recent anti-inflammatory prevention trial (ADAPT) was designed to address these two key problems. First, the ADAPT uses an unprecedented prophylactic approach, and includes patients from populations at high risk of developing AD, but who have not yet been diagnosed with the condition. Second, the ADAPT will investigate two basic types of NSAID: a non selective COX-1/COX-2 inhibitor (naproxen) and a selective COX-2 inhibitor (celecoxib). Thus, this study is designed to address the current state of the art in AD therapeutics, and promises to yield invaluable insight into the relationship between NSAIDs and AD.

Anti-inflammatory drugs have potential neuroprotective effects that may slow the progression of AD, but these compounds are not likely to produce short-term improvements in symptoms. Thus, traditional clinical trial designs and clinical outcome measures that have been employed in determining the clinical efficacy of the cholinesterase inhibitors and other symptomatic drugs are unlikely to be useful for testing anti-inflammatory compounds. The specific nature of the optimal clinical trial for demonstrating the efficacy of NSAID treatment in AD depends on the goal of treatment and the type of patients to be studied. Possible treatment goals may include slowing disease progression in diagnosed AD patients, reducing diagnosis time in individuals with mild cognitive impairment, and preventing AD in cognitively normal, elderly individuals. Addressing each of these treatment goals requires different study subjects as well as different outcome measures that are optimally sensitive to clinical changes in these different subject populations. A theoretically optimal clinical study design should include 10,000 healthy subjects, aged >65, evaluated by WEB for at least 5 years. One of the emerging problems is who will sponsor such a trial. Another critical issue is the need to include biological markers of disease severity in the trial design, since an effect on disease progression cannot be demonstrated unequivocally by means of clinical outcomes alone. However, the availability of adequately validated biological markers remains quite limited. Primary prevention trials in which thousands of subjects are treated for years constitute the ultimate test of NSAID efficacy. Although the necessarily large size and high cost of such trials is a
significant barrier to demonstrating primary prevention, current research is focusing on developing more efficient assessment methods for use in AD primary prevention trials.

Researchers at the University of Pittsburgh School of Medicine in Pennsylvania, the Massachusetts General Hospital in Boston, and the Uppsala University PET Center and Karolinska Institute of Sweden have reported significant developments in this area. Scientists explained that – for the first time – they had used an investigational compound to generate images that may show the presence of amyloid plaques in the brains of living AD subjects. Plaques, abnormal accumulations of protein fragments that may contribute to cell damage in AD, could formerly be identified only in autopsy. In tests of nine individuals with AD, the compound could be detected in the brain scans in patterns consistent with the distribution of plaques previously observed in autopsies. Although further research is needed to confirm these preliminary studies, many researchers were excited about the implication of being able to "see" a characteristic feature of Alzheimer pathology in living subjects. If brain imaging can reveal the presence of plaques, technology may play an important role as other researchers test compounds designed to prevent plaque formation or to clear plaques from the Alzheimer brain.

Activated microglia play a key role in the brain’s immune response to neuronal degeneration. The transition of microglia from the normal resting state to the activated state is associated with an increased expression of receptors known as peripheral benzodiazepine (pBDZ) binding sites. Researchers at the MRC Cyclotron Unit, Imperial College and Division of Neuroscience and Psychological Medicine in London, used brain imaging to study expression of these sites in 15 healthy individuals and 8 patients with AD. They found that patients with AD showed a significantly increased number of pBDZ sites in the entorhinal, temporoparietal, and cingulate cortex. The increased pBDZ sites in the AD brain suggest that microglial activation is involved in the pathogenesis of the disease and that it is now possible to monitor the progression of the immune response in the brains of living patients. These new technological opportunities may prove extremely advantageous in selecting vulnerable populations, supporting diagnosis and monitoring the efficacy of drug treatments.

The Editors

M.M., F.B., G.N., P.F.S.