EDITORIAL

Immunotherapy for Alzheimer Disease

The Promise and the Problem

IMMUNIZATION THERAPY FOR ALZHEIMER DISEASE (AD) entered the realm of possibility with the startling publication in 1999 by Schenk et al[1] of the successful immunization of transgenic mice carrying a human mutant gene for the amyloid precursor protein, causal of early onset AD,[1,2] that resulted in a striking reduction in brain amyloid burden with reduced gliosis and dystrophic neurites in immunized β-amyloid$_{(1-42)}$ (Aβ$_{[1-42]}$)–transgenic mice. As a result of the highly positive reduction of amyloid burden in Aβ$_{(1-42)}$-immunized transgenic mice with improved behavior and memory,[3,4] a phase II double-blind, placebo-controlled, multicenter study was conducted to evaluate safety, tolerability, and pilot efficacy of AN1792 (Aβ$_{[1-42]}$) administered with AS21 adjuvant in 372 patients with mild to moderate AD. Unfortunately, this study had to be stopped owing to the development of meningoencephalitis associated with AN1792 immunization in 18 of 300 immunized patients. By the time the study was discontinued, 24 patients had received 3 immunizations, and 274 patients had received 2 immunizations. There was evidence of some benefit to patients who received immunotherapy immunizations, with improvement in some neuropsychological test scores and in enhanced quality-of-life scores.[5-8]

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In this issue of the ARCHIVES, O'Toole et al[9] describe candidate biomarkers of response to immunotherapy using the GeneChip microarray technology (Affymetrix Inc, Santa Clara, Calif) to explore a pharmacogenomic study of the preimmunization gene expression patterns of peripheral blood mononuclear cells of patients enrolled in the AN1792 study. The objective was to identify gene expression patterns that would serve as biomarkers to assess the potential risk of developing meningoencephalitis, and also to determine the preimmunization probability of significant antibody synthesis that could have a therapeutic effect in lowering brain amyloid burden levels.

O'Toole and colleagues report that the selection criteria for association for meningoencephalitis was made with an analysis of sequences from 689 genes and 8 unmapped sequences, identifying an association between preimmunization gene expression profiles and the postimmunization development of clinical meningoencephalitis. Of note, genes associated with apoptosis and proinflammatory processes, and the tumor necrosis factor pathway in particular, were found to be associated with the occurrence of meningoencephalitis. Further, O'Toole and colleagues found that genes related to tumor necrosis factor/Fas, transforming growth factor β, and p53 pathways, central pathways in the control of the immune system, were highly represented with genes associated with the control of apoptosis. Notably, the gene that was most highly associated (*FDR*=0.004, unadjusted $P<.001$, odds ratio=230) was *STAT1*, a gene highly expressed in a proinflammatory signal transduction pathway. High expression levels of *STAT1* in peripheral blood mononuclear cells prior to immunization had a high level of risk of postimmunization meningoencephalitis. Conversely, a low expression level of *HEAB* was significantly associated with a risk of clinical meningoencephalitis (odds ratio=.0001). Further, O'Toole and colleagues conducted a pairwise combination logistic regression approach to determine 2-gene combinations that best identified all of the patients who developed meningoencephalitis as opposed to those who did not develop meningoencephalitis. One of the genes in the 2-gene combination was either *NPUKP68* or *STAT1* for 18 of the top 20 2-gene combinations. Thus, these 2 genes seem to be the outstanding biomarkers for risk of meningoencephalitis.[9]

In this study,[9] those patients who had the best possibility of generating a significant immunoglobulin response were correlated with expression patterns of genes concerned with protein synthesis. An additional set of genes that participated in translational events was also significant in predicting postimmunization antibody response. In general, immunoglobulin responsiveness to immunization was associated with up-regulation of genes concerned with protein synthesis, protein trafficking, DNA recombination, DNA repair, and cell cycle. It is possible that immunoglobulin nonresponders described in this study could be related to being elderly, with an associated reduced responsiveness to immunization that is associated with age.[10-12]

O'Toole and colleagues have thus identified preimmunization genes in this genomic study that placed patients at risk for postimmunization meningoencephalitis related to proinflammatory and apoptotic cascades of gene up-regulation and expression. Immunoglobulin responsiveness to immunization best correlated with overall robust levels of gene transcription and protein synthesis, independent of inflammatory gene expression.

These are critical observations, and they are evidence of the power and precision of a genomic analysis that can predict disease and, by so doing, potentially prevent it. The era of genomic neurology has arrived, and it

is potentially limitless in identifying at-risk persons for complex multifactorial, polygenetic neurological disease by identifying gene sets that have abnormal expression patterns associated with and predictive of future neurological disease. As shown in the study by O'Toole and colleagues, a genomic analysis of a specific subset of gene expression patterns can also provide predictive value of a positive therapeutic response, and also of potential significant adverse effects of therapy. This is a landmark study that serves as a model for future genomic approaches for the prediction of neurological disease, positive responses to specific therapies, and predictive probabilities for therapeutic concerns. The field of genomics signals the advent of predictive neurological diagnosis and the effective implementation of genomically determined, specific therapies.

The Aβ immunization for AD is a bold new therapeutic approach with great potential.[13] Active vaccination with Aβ peptide as the vaccinating agent may not be feasible owing to the activation of cytotoxic T cells that are causal of meningoencephalitis. However, gene vaccination with the $A\beta_{(1-42)}$ complimentary DNA in a plasmid vector has been shown to generate high titers of anti-$A\beta_{(1-42)}$ antibody in the AD transgenic mouse model without the activation of cytotoxic T cells.[14] Thus, $A\beta_{(1-42)}$ gene vaccination for AD remains another viable option.

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