＜シンポジウム 01―4＞神経内科における大規模臨床治験

Familial Amyloid Polyneuropathy: Diflunisal

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Transthyretin (TTR) is a homotetrameric serum and cerebrospinal fluid protein that transports both thyroxine (T_4) and the retinol-retinol binding protein complex (holoRBP). Rate-limiting tetramer dissociation and rapid monomer misfolding and misassembly of variant TTR results in familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy (FAC), or familial central nervous system amyloidosis. Analogous misfolding of wild-type TTR results in senile systemic amyloidosis (SSA) characterized by sporadic amyloidosis in elderly populations. With the availability of genetic and immunohistochemical diagnostic tests, patients with TTR amyloidosis have been found in many nations worldwide. Recent studies indicate that TTR amyloidosis is not a rare endemic disease as previously thought. The only effective treatment for the familial TTR amyloidoses is liver transplantation;however, this strategy has a number of limitations, including a shortage of donors, a requirement for surgery for both the recipient and living donor, and the high cost. Furthermore, a large number of patients are not good transplant candidates. Recent studies focused on the *TTR* gene and protein have provided insight into the pathogenesis of TTR amyloidosis and suggested new strategies for therapeutic intervention. TTR tetramer (native state) kinetic stabilization by small molecule binding, immune therapy, and gene therapy with small interfering RNAs are promising strategies based on our understanding of the pathogenesis of TTR amyloidosis. Among these, native state kinetic stabilization by diflunisal and Fx-1006A (tafamidis), a novel therapeutic strategy against protein misfolding diseases, are currently in Phase II/III clinical trials and evidence is accumulating that these drugs are effective in preventing disease progression. In an open label clinical trial, diflunisal (250 mg bid) was well tolerated by most FAP patients and increased serum TTR concentration and stability. In addition, deterioration rate of clinical FAP score in patients who are taking diflunisal was slow (+0.78/year) compare to natural course of FAP (+7/year). A randomized controlled trial, for which patients are now being enrolled internationally, is necessary to determine the clinical effects of diflunisal on FAP.

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