SHOULD COMBINATION TREATMENT WITH CHE-I AND MEMANTINE BE STARTED AS EARLY AS POSSIBLE? (YES)

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Background

Given the ongoing population aging we are currently dramatically confronting with a genuine "Alzheimer's crisis". The main challenge deals with the critical lack of disease modifying drugs. The FDA approved cholinestherase inhibitors – ChEIs (tacrine, rivastigmine, galantamine, donepezil) and memantine (NMDA receptor antagonist) may only temporarily relieve some symptoms and slow their progression. The improvement of their modest efficacy is strongly correlated with early diagnosis and treatment initiation, which may allow the necessary time for treatment personalization and a better management of symptoms if attacked from their mild stage. A significant fact is that memantine may influence not only cognitive, but also mood and behavioral correlates of Alzheimer's disease (AD). A promising approach seemed then to combine ChEIs and memantine treatments in order to synergistically target the dysfunctions of two neurotransmitter systems critically involved in cognition: the cholinergic system and the GABAergic one. In spite of a (still) ongoing assessment of this combination, the emerging question is the enhancement of its clinically significant effects by initiating the treatment as early as possible.

Method

The analysis of recent scientific reports and the outcomes of our observational studies plead for a positive answer to the above, last question.

Results

The arguments pleading for the benefits of initiating as early as possible the combined treatment with ChEI and memantine are overviewed.

First, Alzheimer's dementia (AD) is a plurifactorial disease in which challenging environmental factors trigger the disease's onset by acting on inner, predisposing abnormalities, and requires plurifactorial therapeutic interventions. Simultaneous actions of supporting cholinergic dysfunctions by means of AChEI and inhibiting NMDA, 5-HT3, and nicotinic receptors by memantine that also enhance cerebral glucose utilization and inhibit Abeta-induced neurodegeneration, provide the explanatory background for the beneficial effects of their combination reported in the literature. Generally, ChEIs monotherapy has shown modest symptomatic stabilization/improvement for up to 12 months, but there are also studies that document a longer-term action. Memantine monotherapy also exhibited modest cognitive and functional benefits, but for all AD stages. It can additionally influence mood and behavioral symptoms and the evolution toward high dependence degree. Some studies also document its indirect beneficial effects on caregivers. Nor AChEIs neither memantine attack the underlying pathological mechanisms of the disease and its two main physiopathological features: progressive synaptic loss and neuronal death. The newest approaches concerning serotonergic antidepressants, M1 muscarinic and nicotinic agonists, M2 antagonists, anti-inflammatory drugs, monoamine oxidase inhibitors, secretase inhibitors, cerebrolysine, statins, cholesterol-lowering drugs, amyloid-beta-peptide vaccination, metal chelators, may complete in the future the picture of the adjunctive symptomatic therapy in AD. Until then, the possibility to synergistically modulate both acetylcholine and glutamate neurotransmission is a novel, important treatment strategy for mild to moderately severe AD. As documented by Francis (2003), the up regulation of N-methyl-D-aspartate (NMDA) receptors may result in cholinergic dysfunction. In this context memantine acts as neuroprotecting drug.

Second, a critical matter in this adjunctive therapeutic approach is treatment personalization. There are certain differences in the effects exerted by the AChEIs actually in use. For example rivastigmine inhibits both acetyl cholinesterase and butyrylcholinesterase (Giacobini 2004), while, unlike other AChEIs, galantamine is equally a nicotinic receptor modulator with long-term symptomatic effects on cognition, functionality and behavior. The benefit of switching from one agent to another (Scarpini et al., 2003) is to be taken into account including in the combined treatment with memantine.

The third and most important argument relates to the early detection of the disease, able, among other, to allow sufficient time for treatment personalization and adjustment. Vidal JS et al. (2008) define "a temporal relationship between the onset of memantine treatment and the stabilization of psychotropic drugs" on a cohort of 4,600 patients. Wilcock GK et al. (2007) point out that the severity of cholinergic dysfunctions directly correlates with advanced stages of the disease, while Matthias WR (2006) points out that early therapy is beneficial for delaying symptoms worsening. Farlow and Cummings (2007) also infer that the main steps of AD management are early diagnosis, early ChEI treatment initiation as standard

first-line therapy, capable to facilitate stabilization or improvement of cognitive and functional symptomatology, while memantine may be used as monotherapy in severe AD, or combined with a ChEI in moderate Alzheimer's disease. Despite the bulk of actual references that support ChEI and memantine combination as a fruitful approach of AD therapy, especially for the mild to moderate stages of the disease, those containing evidence-based arguments for the high importance of early treatment initiation are still scarce, and more work in the field is still needed.

Actually, the huge technological progress supports an unprecedented development of early detection markers, especially molecular (Abeta 41-42, tau, B12) and imagistic (PET scan, for hippocampal atrophy or parieto-temporal hypometabolism), for amnestic MCI and prodromal AD. As partner in the DESCRIPA study fulfilled under EADC's auspices we overview the main results of a prospective cohort study related to the prognostic value of CSF markers in patients with subjective cognitive or mild cognitive impairment (Visser PJ et al., 2009), as well as related to the development of screening guidelines and clinical criteria for predementia Alzheimer's disease (Visser PJ et al., 2008).

Conclusions

Multifactorial therapeutic attempt is crucial for diseases like AD. The synergistic therapeutic approach of cholinergic and GABAergic dysfunctions in AD is a right way to be pursued and developed. Other pharmaceutical agents, but also non-drug interventions, will add soon to the actual picture of AD holistic therapeutic approach. Optimization and treatment personalization of ChEI-memantine combination depend on the stage when the patient is referred to the specialist and his/her particular clinical phenotype. Early disease detection (in amnestic MCI and prodromal AD phases) and the earliest treatment initiation are crucial for symptoms improvement and slowing of their worsening rate.