

Combination Therapies in Alzheimer's Disease

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Alzheimer's disease (AD) is the leading cause of dementia worldwide. Until now, available therapeutic agents for AD treatment only provide symptomatic treatment. Since AD pathogenesis is multifactorial, use of a multimodal therapeutic intervention addressing several molecular targets of AD-related pathological processes seems to be the most practical approach to modify the course of AD progression. It has been demonstrated through numerous studies, that the clinical efficacy of combination therapy (CT) is higher than that of monotherapy. It is indeed difficult to combine several pharmacophores into a single molecule. It is essential to carry out long-duration randomized controlled trials to establish whether CT delays disease progression in early AD stages. Other factors also need to be assessed in CT, such as its potential neuroprotective effects, cost-effectiveness, and a more exhaustive estimation of its potential benefits on the patients at the end-stage of AD.

Keywords: Alzheimer's disease ; combination therapy ; memantine ; cholinesterase inhibitors

1. Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disorder, thus treating AD patients still remains a challenge. Presently, the approved AD treatments are limited to memantine and cholinesterase inhibitors (ChEIs) or the combination of these two agents. Most of the newly tested drugs failed in phase III trials due to their incapacity to meet the target efficacy, even though they exhibited promising results in their initial studies. The complex nature of AD is considered as one of the main reasons for the high failure rate of these new treatments ^[1]. Additionally, another reason for this high failure rate is our incomplete understanding of the numerous mechanisms involved in AD development and following neurodegeneration and the potential lack of efficacy of the available drugs. Since the combination of ChEIs and memantine have encountered less success in case of AD treatment, thus targeting multiple pathways to treat AD has better chances of success. Therefore, additional studies examining rational combinations of agents ought to be continued.

2. Therapy

As add-ons to standard-of-care therapy, multiple current studies are currently exploring the effects of symptomatic agents or disease-modifying therapies. Nonetheless, a combination of two or more agents targeting different mechanisms and providing synergistic effects has better chances to treat AD. However, only a limited number of these agents are under clinical trials ^[2].

The use of ChEI-memantine combination therapy (CT) in patients with mild-to-moderate AD has not been demonstrated conclusively. Randomized controlled trials (RCTs) exhibited similar short-term performances for CT and monotherapy ^[3], while long-term observational analyses support the effectiveness of the CT to decrease the rate of cognitive decline and the level of dependence and denote that CT is more effective when started early and maintained for a long period ^{[4][5][6][7]}. Thus, long-duration RCTs are needed to confirm whether a CT applied in the early stages of AD can delay the progression of this disease. The potential long-term benefits of a CT should be more apparent after two years when the rate of deterioration is more evident ^[8].

CT might also diminish the doses used of the individual drugs with an eventual decrease in the costs and the side effects of the treatments. The design of adaptive and innovative clinical trials might be interesting for the potential development of therapeutic combinations over the disease progression, using one set of agents for preclinical AD, another for early-stage AD, and yet another for AD dementia. Collectively, challenges in AD treatment have guided the current therapeutic approaches toward the evaluation of new drugs as an add-on to standard-of-care and the repurpose of currently approved therapeutic agents which are indicated for other therapeutic conditions as well as the combination of agents that target different pathways ^[9].

Even though most of the add-on trials with potential disease-modifying drugs have failed so far, results in this area indicate that success may be further obtained, predominantly in case of neurotrophic agents and anti-amyloid strategies. Cerebrolysin, anti-A β vaccines and insulin may constitute beneficial agents which require additional studies in the future. Combinations of anti-amyloid and/or anti-tau interventions with neurotrophic agents have not yet been investigated but can lead to additive or synergistic effects. Further studies with drugs in prodromal or early AD stages may require long follow-up periods to prove their efficacy as the rates of progression of the disease and the clinical deterioration of patients are highly variable and rather slow [2].

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