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Featured Article

A multicenter, randomized, placebo-controlled trial for cilostazol in patients with mild cognitive impairment: The COMCID study protocol

Satoshi Saito[a,b,*], Shinsuke Kojima[c], Naoya Oishi[d,e], Ryosuke Kakuta[f], Takakuni Maki[b], Fumihiko Yasuno[g], Kazuyuki Nagatsuka[f], Haruko Yamamoto[h], Hidenao Fukuyama[d,e], Masanori Fukushima[c], Masafumi Ihara[a,f,*]

[a]*Department of Regenerative Medicine and Tissue Engineering, National Cerebral and Cardiovascular Center, Suita, Japan*
[b]*Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan*
[c]*Department of MediScience, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan*
[d]*Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan*
[e]*Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto, Japan*
[f]*Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center, Suita, Japan*
[g]*Department of Psychiatry, Nara Medical University, Kashihara, Japan*
[h]*Center for Advancing Clinical and Translational Sciences, National Cerebral and Cardiovascular Center, Suita, Japan*

Abstract

Introduction: There are currently no effective treatments preventing conversion from mild cognitive impairment (MCI) to Alzheimer's disease. Cilostazol is a selective type-3 phosphodiesterase inhibitor that ameliorates accumulation of amyloid-β and has prevented cognitive decline in rodent models. Furthermore, cilostazol is known to suppress platelet aggregation, protect vascular endothelia, dilate vessels, and increase cerebral blood flow. Beneficial effects have also been shown in observational cohort studies, demonstrating the need for a prospective clinical trial.

Methods: The Cilostazol for prevention of COnversion from MCI to Dementia (COMCID) study is a double-blind, randomized phase II study of patients with MCI. Participants will receive cilostazol or placebo for 96 weeks. The primary objective is to evaluate whether cilostazol slows down cognitive decline measured by the Mini-Mental State Examination. Secondary objectives are assessing time to conversion from MCI to dementia and assessing incremental changes in several psychological assessment scales.

Discussion: The COMCID trial will identify the therapeutic potential of cilostazol. This trial, which is based on a drug repositioning strategy, may aid the development of a neurovascular treatment for neurocognitive disorders.

Keywords: Alzheimer's disease; Cilostazol; Clearance; Clinical trial; Drug repositioning

1. Introduction

Epidemiologic investigations have proposed that strict control of vascular risk factors is an effective preventative strategy for dementia because of the close relationship between Alzheimer's disease (AD) and cerebrovascular disease (CVD) [1]. AD is thought to result from an imbalance between production and clearance of amyloid-β (Aβ), and

This trial (institutional protocol number: TRINEU1321) was registered as ClinicalTrials.gov NCT02491268 (https://clinicaltrials.gov/ct2/show/NCT02491268) and UMIN Clinical Trials Registry (UMIN-CTR) UMIN000017764 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000020389).

*Corresponding authors. Tel.: +81-6-68335012; Fax: +81-6-68355137.

E-mail address: saitosa@ncvc.go.jp (S.S.), ihara@ncvc.go.jp (M.I.)

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CVD is related to excessive Aβ production and elimination failure [2]. Decreased cerebral blood flow is closely related to CVD and seems to modulate amyloid precursor protein cleavage enzymes, such as β- and γ-secretase, leading to increased Aβ production [3]. A large proportion of Aβ clearance takes place through vascular-mediated systems, via active transport across the blood-brain barrier, perivascular lymphatic and paravascular glymphatic drainage networks, all of which can be disturbed by CVD [4]. Familial cases of AD may be, at least in part, attributable to excess Aβ production. However, insufficient Aβ clearance is more crucial in cases of sporadic AD [5]. Therefore, researchers have increasingly sought to address the problem of Aβ elimination in AD therapy [6].

The vasoactive drug cilostazol inhibits type-3 phosphodiesterase and is expected to promote Aβ clearance. In rodent models exhibiting Aβ accumulation, administering cilostazol prevented Aβ deposition and improved cognitive function by increasing hemodynamic reserve and facilitating perivascular drainage of Aβ [7]. The brain parenchyma is devoid of a conventional lymphatic system, although the lymphatic vessels were recently found to exist along meningeal vessels [8]. Interstitial fluid and solutes, including Aβ, are cleared through a perivascular drainage route, which is formed by two basement membranes in the walls of cerebral arteries [9]. Cilostazol was found to facilitate this clearance system in vivo [7]. Furthermore, experimental studies indicate that cilostazol reduces Aβ production and suppresses tau phosphorylation by inhibiting glycogen synthase kinase 3β, via enhancement of casein kinase 2α/silent information regulator 1 phosphorylation, in vitro [7,10,11]. Whether such effects are viable in AD and mild cognitive impairment (MCI) patients is not yet clear as only a minor fraction of cilostazol passes through the blood-brain barrier [12].

Cilostazol is currently prescribed in Asia, Europe, and the United States as an antiplatelet drug for symptomatic treatment of peripheral arterial disease. It is also used in Asia for the secondary prevention of ischemic stroke. The second Cilostazol Stroke Prevention Study for patients with cerebral infarction showed that hemorrhagic stroke was significantly less frequent with cilostazol treatment than with aspirin [13,14]. The prevention of cerebral hemorrhage may be explained by its protective effects on vascular endothelial cells [15]. Furthermore, cilostazol is known to dilate blood vessels, leading to increased cerebral blood flow [16]. These results suggest that cilostazol could be suitable for patients with both AD neurodegeneration and CVD.

Favorable effects have been reported in observational clinical studies, which demonstrated efficacy of cilostazol in patients with MCI [17], donepezil-treated patients with clinically probable AD [18,19], and AD with CVD [20]. These results have thus highlighted the need for a comprehensive prospective cohort study to determine whether cilostazol helps preserve cognitive function in patients with MCI.

2. Methods

2.1. Study design

The investigator-initiated Cilostazol for prevention of COnversion from MCI to Dementia (COMCID) trial is a double-blind, placebo-controlled, randomized early phase II study aimed at evaluating the efficacy and safety of cilostazol in patients with MCI (Fig. 1). Two hundred MCI patients will be randomly assigned to cilostazol or placebo control arms. The allocation ratio is 1 to 1.

2.2. Study objectives

The primary objective of the study is to evaluate the efficacy of cilostazol in patients with MCI in preserving cognitive function measured by the Mini-Mental State Examination (MMSE). The secondary objectives are to evaluate the efficacy of cilostazol in assessing time to conversion from MCI to "all-cause dementia," as well as changes in the Clinical Dementia Rating–Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale–cognitive sub-scale (ADAS-cog) 14, Wechsler Memory Scale-Revised (WMS-R) Logical Memory part II, and Alzheimer's Disease Cooperative Study–Mild Cognitive Impairment–Activities of Daily Living (ADCS-MCI-ADL). Another secondary objective is to explore the efficacy of cilostazol on the hippocampal atrophy, measured by brain magnetic resonance imaging (MRI).

2.3. Enrollment

MCI patients are recruited from 15 high-volume centers for patients with dementia in Japan. Potential participants will undergo screening assessment to confirm eligibility (Fig. 2). Blood examinations and MRI investigation for confirming eligibility will not be scheduled in the COMCID trial as only MCI patients who have undergone sufficient laboratory tests for clinical purposes before informed consent about this trial can participate. These laboratory examinations are routinely performed in all trial sites. Pure vascular MCI patients are ineligible, whereas patients with coincidental cerebral infarctions or white matter changes not likely to wholly explain their cognitive dysfunction are eligible. Based on the core clinical criteria stated in the National Institute on Aging-Alzheimer's Association classification [21], MCI is diagnosed when individuals meet the following criteria:

- cognitive concern reflecting a change in cognition reported by the patient, informant, or clinician
- objective evidence of impairment in one or more cognitive domains
- preservation of independence in functional abilities
- not demented

In addition, MMSE scores between 22 and 28 (inclusive) and CDR scores of 0.5 are required for provisional registration (Fig. 1). Results from MMSE and CDR will be reviewed by an independent central psychological review board. If the patient is judged to be eligible, the review board will submit