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Clinical Study Protocol

An Open-Label Feasibility Trial of Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Major Depressive Episodes

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Repetitive transcranial magnetic stimulation (rTMS) has been reported to be a new treatment option for treatment-resistant depression. In Japan, there has been limited research into its feasibility, efficacy, and tolerability. We have launched a trial of rTMS for treating medication-resistant major depressive disorder and bipolar depression. We are investigating low-frequency rTMS to the right dorsolateral prefrontal cortex and traditional high-frequency rTMS to the left dorsolateral prefrontal cortex, in 20 patients. The primary outcome of the study is the treatment completion rate. This study will provide new data on the usefulness of rTMS for treatment-resistant depression in Japan.

Key words: repetitive transcranial magnetic stimulation, depression, treatment resistance, low frequency

Major depressive disorder (MDD) and bipolar disorder (BD) are prevalent psychiatric conditions. They account for almost a half of the disability-adjusted life-years caused by mental and substance use disorders, and are one of the leading causes of disease burden [1]. In Japan, epidemiologic studies have revealed that the 12-month and lifetime prevalence of mood disorders (including BD) are 2.3% and 6.5%, respectively [2].

Treatment-resistant major depressive episode (TR-MDE) is a common issue in clinical practice [3]. Recently, repetitive transcranial magnetic stimulation (rTMS) has been reported to be an effective and well-tolerated antidepressant treatment for TR-MDE [4–8]. rTMS is a noninvasive technique stimulating the cerebral cortex, altering cortical and subcortical function, and has been reported to have therapeutic effects in several neuropsychiatric disorders, including mood disorders [9]. rTMS for the treatment of MDD has been approved in North America, Latin America, Europe, Australia, New Zealand, Israel, and Korea, among other countries. Typically, one of two equally effective typical stimulation protocols are used [10]; traditional high-frequency rTMS to the left dorsolateral prefrontal cortex (HF-LDLPFC), as approved by the U.S. Food and Drug Administration; or an experimental low-frequency rTMS to the right DLPFC (LF-RDLPFC), which has fewer side effects. The effect size for rTMS antidepressant efficacy is at least comparable to those of antidepressant medications, even though previous studies included only

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treatment-resistant or treatment-intolerant depressed patients [11]. In contrast to major depressive episode (MDE) in MDD, on which the majority of published rTMS studies have focused, there have been few studies investigating the effect of rTMS on MDE in BD [12–15].

In Japan, no rTMS device for treatment use has been approved by the Ministry of Health, Labour and Welfare, which has resulted in its off-label use. Therefore, there have been only limited data available on the efficacy and tolerability of rTMS for the treatment of MDE in Japan [16–21]. To date, there have been no reports of the feasibility and efficacy of the rTMS parameters used in the present study in Japan and other parts of Asia.

This study will examine the feasibility and preliminary efficacy of rTMS for TR-MDE in Japan. The primary outcome of the study is treatment completion rate. Secondary outcome measures include assessment of the severity of depression and mania.

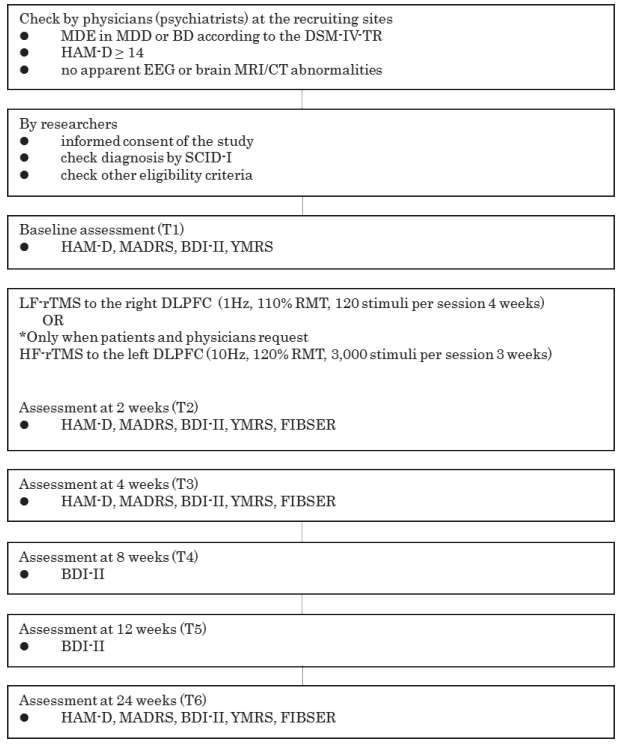

Fig. 1 Flow chart of the trial design. MDE, major depressive episode; MDD, major depressive disorder; BD, bipolar disorder; HAM-D, Hamilton Depression Rating Scale; EEG, electroencephalogram; SCID-I, Structured Clinical Interview for DSM-IV-TR Axis I Disorders; MADRS, Montgomery-Åsberg Depression Rating Scale; BDI-II, Beck Depression Inventory-II; YMRS, Young Manic Rating Scale; FIBSER, Frequency, Intensity, and Burden of Side Effects Rating; LF, low frequency; HF, high frequency; DLPFC, dorsolateral prefrontal cortex; RMT, resting motor threshold.

Endpoints

The primary outcome of this study is the treatment completion rate. We use the following criteria for terminating the intervention: patient's request to terminate treatment, the occurrence of a serious adverse event, detection of pregnancy, and a physician's decision based on risk or other reasons. Treatment completion is defined as the patient undergoing prescribed sessions without termination of treatment. Secondary outcome measures include scores on the HAM-D 17-item version [22], the Montgomery-Åsberg Depression Rating Scale (MADRS) [23], the Beck Depression Inventory-II (BDI-II) [24], the Young Manic Rating Scale (YMRS) [25], and the Frequency, Intensity, and Burden of Side Effects Rating scale (FIBSER) [26]. These parameters are assessed at baseline (T1), 2 (T2), 4 (T3), and 24 weeks (T6). At 8 (T4) and 12 weeks (T5), only the BDI-II is administered. Fig. 1 shows an overview of the study design.

HAM-D. The HAM-D is the most widely used observer-rated scale to assess level of depression in clinical research. The original version, developed in 1960, contains 17 items [22]. We use the Japanese version of the Structured Interview Guide for Combined Rating of HAM-D and the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C), which have been used in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [27].

MADRS. The MADRS is a common observer-rated 10-item scale to assess level of depression [23]. We use the Japanese version of the MADRS using a structured interview guide for MADRS (SIGMA), which has been shown to have good inter-rater reliability [28].

BDI-II. The BDI-II is a 21-item self-report instrument that assesses level of depression [24]. Good reliability and validity have been reported for the Japanese version [29].

YMRS. The YMRS is the most frequently used observer-rated 11-item scale to assess level of mania

or hypomania [25]. We use the Japanese version of YMRS-J, with good inter-rater reliability [30].

FIBSER. FIBSER was originally used in the STAR*D study as a global rating scale for side effects [26]. This is an observer-rated scale that consists of three domains evaluating the frequency, intensity, and severity of side effects. The Japanese translation has not been validated by back-translation.

Eligibility Criteria

On April 1, 2014 we commenced a single-arm, prospective, non-randomized, non-comparative, open-label, multicenter, phase I and II trial. Patient enrollment will finish on October 31, 2016.

The inclusion and exclusion criteria for the present study are listed in Table 1. Written informed consent must be obtained from the patient before any screening or inclusion procedure. This study is being conducted in compliance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study has been approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and the Okayama University Hospital, Ethics Committee (approval numbers m22002 and 25-8, respectively). This trial has been registered with the UMIN Clinical Trials Registry (registration number 000013553).

The recruiting sites are Okayama University Hospital and Okayama Psychiatric Medical Center. Attending physicians (psychiatrists) screen patients for eligibility using a diagnosis of MDE according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revision (DSM-IV-TR) [31], and assess the severity of their depression using the Hamilton Depression Rating Scale (HAM-D) [22]. The attending physicians also check for abnormalities using electroencephalography, and either brain magnetic resonance imaging or computed tomography. Researchers confirm diagnoses using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) [32] and all eligibility criteria, then seek written informed consent from eligible patients.

Table 1 Patient eligibility

Inclusion criteria
DSM-IV-TR diagnosis of major depressive disorder (MDD) or bipolar disorder (BD)
Hamilton Scale for Depression 17-item score: 14 or more
Medication resistance due to ineffectiveness or intolerable side effects
Insufficient clinical improvement of MDD from at least 2 antidepressant trials
Insufficient clinical improvement of BD from lithium or lamotrigine and atypical antipsychotic treatment
Capability to give informed consent
Aged 20 years old or more
Exclusion criteria
Other Axis I disorders
Axis II disorders
Seizure-inducing disease (brain tumor, head injury, etc.)
Neurologic disorder, organic brain disorder
History of seizure
Paroxysmal electroencephalogram abnormality
Pregnancy
Ferromagnetic material in head (except oral cavity)
Patients with a pacemaker
Active suicidal ideation
Stupor
Treatment with electroconvulsive therapy within the past month
Depression related to physical disease or drug use
Family members of researchers
Patients likely to change to another hospital within 6 months
Patients not appropriate for participation in the study as judged by the physician
Patients who do not understand Japanese

Treatment Methods

rTMS is administered using a Magstim Super Rapid stimulator® (Magstim Co., Whitland, U.K.) and a hand-held, focal 70-mm figure-of-eight coil. Prior to the commencement of every rTMS session, single-pulse TMS is used to measure the resting motor threshold (RMT) for the abductor pollicis brevis using the standard method [33]. The stimulation area during the rTMS sessions is defined by a point 5 cm anterior to that required for maximum stimulation of the abductor pollicis brevis.

First, researchers explain the risks and benefits of both LF-RDLPFC and HF-LDLPFC to the patient and their physician. Patients, by default, receive LF-RDLPFC treatment, which has been suggested to be equally effective and more tolerable compared with HF-LDLPFC treatment [10]. In addition, as shown in Fig. 2, the treatment time is shorter in LF-RDLPFC than HF-LDLPFC, involving a lower burden on

patients. Therefore, only when requested by the patient and their physician, is HF-LDLPFC administered instead of LF-RDLPFC. Fig. 2 shows the stimulation protocol of LF-RDLPFC and HF-LDLPFC. For LF-RDLPFC, two 60-sec trains are applied at 1 Hz and at 110% of RMT, with a 120-sec inter-train interval (total of 120 stimuli per session). LF-RDLPFC stimulation sessions are performed daily on working days for 4 weeks. For HF-LDLPFC, 75 4-sec trains are applied at 10 Hz and at 120% of RMT with a 26-sec inter-train interval (total of 3,000 stimuli per session). During the first week only, treatment intensity is reduced to 110% RMT for tolerability. HF-LDLPFC stimulation sessions are performed daily on working days for 3 weeks. In determining the protocol, we reviewed prior trials and assessed the parameters with a favorable efficacy-tolerability balance [34-39].

Throughout the study, patients may receive their usual treatment, including psychiatric drugs and psychotherapy, but not electroconvulsive therapy or transcranial direct current stimulation.

Statistical Consideration

We will report baseline characteristics and results for qualitative analysis. To evaluate preliminary efficacy, assuming that 30% of patients remit, another 30% respond, the other 30% would not respond or get worse, at least 15 patients will be needed to ensure each category includes at least 5 patients [8, 40]. We determined that a sample of 20 patients is needed, taking into account dispersion. We considered that the sample size would be enough to evaluate the feasibility as the primary outcome of the present study.

This study will show the feasibility and preliminary efficacy of rTMS for TR-MDE in Japan.

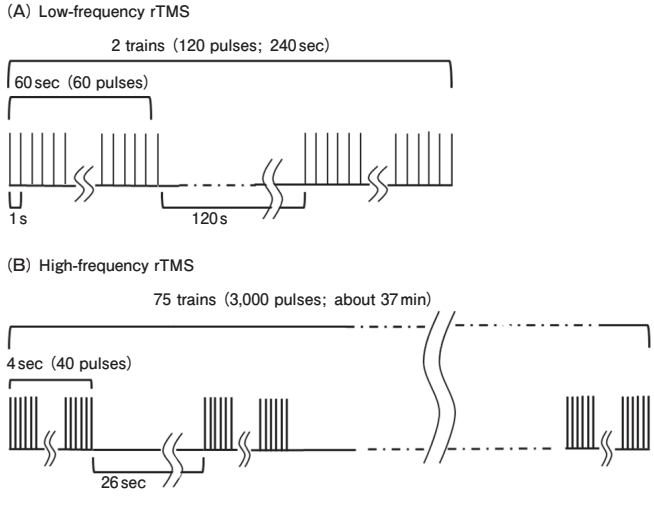

Fig. 2 Stimulation protocol of LF-RDLPFC (A) and HF-LDLPFC (B). rTMS; repetitive transcranial magnetic stimulation.

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