Published in final edited form as:

Am J Geriatr Psychiatry. 2009 August ; 17(8): 682–687. doi:10.1097/JGP.0b013e3181a88423.

Citalopram for continuation therapy following repetitive transcranial magnetic stimulation (rTMS) in vascular depression

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Abstract

Objectives—We previously reported that repetitive transcranial magnetic stimulation (rTMS) produced a response rate of 39.4% among 62 patients with treatment resistant vascular depression. The current study was undertaken to assess the outcome of continuation therapy to prevent relapse among these patients during 9 weeks after completion of rTMS.

Design—Patients were randomly assigned to 18,000 pulses of rTMS given over 3 weeks or sham treatment using double blind methods. Following rTMS, all patients were given 20 mg per day of citalopram for 9 weeks and reevaluated at 3, 6 and 9 weeks.

Setting—Outpatient continuation treatment trial.

Participants—Patients with vascular depression (n=62), as determined by MRI hyperintensities and/or 3 or more clinical risk factors for vascular disease without other major medical illness, were recruited. They had onset of major depression after age 50 and failed at least one trial of antidepressants.

Intervention—Following rTMS or sham treatment, all treatment responders were given citalopram for 9 weeks.

Results—Among the 33 patients given rTMS, 13 responded (i.e. >50% decline in Hamilton Depression Scale score). Of these 13, all completed the 9 weeks of continuation treatment. There were 9 patients who continued to be responders and 4 who had a relapse of depression.

Conclusion—More effective methods are needed to treat elderly patients with treatment resistant vascular depression and to prevent relapse among treatment responders.

Introduction

The vascular depression hypothesis was proposed by Alexopoulos et al. (1) and Krishnan et al. (2) in 1997 and each investigator suggested diagnostic criteria that were based on clinical and radiological findings. The primary features were clinical and/or magnetic resonance imaging (MRI) evidence of vascular disease, onset of depression after age 65 or a distinct change in the course of depressions which began before age 65 (1). In addition, limited depressive ideation, such as guilt, impaired executive function, poor insight, absence of family history of mood disorder and the rare occurrence of psychotic symptoms, were proposed to define this disorder. Data supporting some of these criteria, such as later age of onset, were

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Financial Disclosures: The authors have no financial disclosures relevant to this study. There was no support from pharmaceutical companies or manufactures of rTMS equipment.

NCT00044798: Magnetic Stimulation Therapy for Treating Vascular Depression (rTMS)
<http://clinicaltrials.gov/ct2/show/NCT00044798?term=rtMS&rank=10>

reported by Krishnan et al. (2) Similarly, we have recently found that family history of psychiatric disorder was significantly less common in vascular compared with non-vascular depressions (3).

In addition to these diagnostic criteria, some studies have suggested that vascular depression is less responsive to antidepressant treatment than non-vascular late life depression (4). However, more recent studies have found that treatment response was not related to the severity of white matter hyperintensities on MRI and vascular depression patients responded to antidepressant therapy as well as non-vascular patients without evidence of significant cerebrovascular disease (5,6).

We recently examined the response of patients with vascular depression to repetitive transcranial magnetic stimulation (rTMS) (7). This double blind study was done in 2 separate protocols. : The results presented in this paper are from the second experiment described in Jorge et al. (7). The subjects were randomized into active rTMS receiving 15 sessions at a frequency of 10 Hz, with intensity of 110% of the motor threshold during a 6-second period, with a total of 20 trains separated by 1-minute pauses, during a 10-day period and sham rTMS with the same schedule of administration. All stimulations were over the left prefrontal cortex. Following the treatment trial, all subjects were given non-blinded 9 week continuation treatment utilizing citalopram 20 mg/day. We undertook this continuation therapy to determine whether response would continue or whether some patients would relapse during the 9 weeks of treatment.

Methods and Materials

Patients studied

Patients with onset of major depression at age 50 or older, with a history of subcortical stroke or at least 3 of the following cardiovascular risk factors: arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking, were recruited from the outpatient and inpatient units of the Department of Psychiatry at the University of Iowa Hospitals and Clinics as well as through newspaper advertisements in metropolitan areas around the state of Iowa. All patients had major depression during the current depressive episode but some were partially treated and only met DSM-IV-TR criteria for minor depression (i.e. research criteria) at the time of enrollment in the study. In addition, evidence that the current episode of depression was unresponsive to at least one course of treatment with antidepressants given in adequate doses was required. Adequate antidepressant treatment was defined as a score of 3 or greater on the Antidepressant History Form (8). If the patient was taking antidepressants when enrolled in the study, the therapy was tapered and discontinued for at least 4 days, except for fluoxetine for which a period of 3 weeks was necessary, before initiation of rTMS. Exclusionary criteria have been described in our prior publication (7) including severe coexistent medical illness or psychotic depression. The study was approved by The University of Iowa Institutional Review Board. Written and informed consent were obtained from all subjects after presentation of consent form materials and a discussion of the studies procedures, risks and benefits.

Diagnosis and clinical assessment

The diagnoses of Major and Minor depression were made using the Structured Clinical Interview for DSM-IV (SCID) and DSM-IV diagnostic criteria. The Cumulative Illness Rating Scale (9) was used to assess presence and severity of comorbid medical conditions in each organ system.

The severity of depression was measured using the 17-item Hamilton Depression Rating Scale (HDRS-17) score(10). We have demonstrated in a previous publication that the HDRS

constitutes a valid and reliable measure for severity of depressive symptoms among patients with cerebrovascular disease (11).

The primary outcome parameters for the present study were response and remission rates. Response was defined as a decrease in HDRS-17 total score more than 50% from pretreatment baseline levels to 3 weeks (following rTMS) or 2 weeks following both rTMS and citalopram treatment. Patients with an HDRS-17 score of <8 and who did not meet criteria for major or minor depression were considered to be in remission. Relapse was defined as an increase in HDRS score from 3 weeks (when rTMS was completed) to 12 weeks (when the maintenance trial was finalized) of at least 4 points on the HDRS-17 and meeting criteria for either major or minor depressive disorder at the end of the treatment trial.

Activities of daily living (ADL) were assessed using the Functional Independence Measure. The Functional Independence Measure (FIM) is an 18-item, ADL scale that has been shown to be valid and reliable among patients with cerebrovascular disorders. Higher scores indicate less impairment (12).

Imaging

Magnetic resonance imaging (MRI) was performed on every patient at the time of enrollment in the study, using a 1.5-T scanner (Siemens Avanto; Siemens, New York, NY) from the MRI facility of the University of Iowa Hospitals and Clinics. The details of the imaging protocol were described in our prior publication (7). Four different image sets were acquired for the MRI standard workup: 1) a 3-dimensional, T1 weighted magnetization-prepared rapid gradient echo sequence in the coronal plane; 2) a 2-dimensional proton density weighted turbo spin-echo sequence in the coronal plane; 3) a 2-dimensional T2 weighted turbo spin-echo sequence in the coronal plane; and 4) a 2-dimensional fluid-attenuated inversion recovery sequence in the axial plane.

We used the tools of the locally developed software package (i.e. BRAINS-2; The University of Iowa) to generate data from the 4 image sets (13,14). White and gray matter hyperintensities which appear as hyperintense signals on proton density and T2 weighted images were manually traced. Inter rater reliability for the total volume of deep white matter hyperintensities and subcortical gray matter hyperintensities was assessed between 2 trained operators. For 10 MRIs showing these subcortical changes, the interclass correlation was 0.94.

rTMS treatment

The rTMS protocol involved obtaining investigational device exemption from the US Food and Drug Administration (Investigational Device Exemption # G980216). The rTMS was performed using a commercially available stimulator (Magstim Super Rapid Stimulator; JALI Medical Inc, Wellsey Hills, MA) and 70 mm figure 8 shaped coils, one for active stimulation and a second for sham stimulation. Localization of the stimulation site in the left prefrontal cortex was performed using image normalization to the Talairach coordinate system. A more detailed description of this method is included in our prior publication (7). Treatment was administered during a 10 day period with two sessions per day for five days to achieve a total cumulative dose (TCD) of 18,000 pulses (18K).

Citalopram treatment

Following completion of the rTMS protocol, all patients, regardless of whether they had responded to rTMS treatment, were given 20 mg of citalopram, one pill daily, for the next 9 weeks. Patients were evaluated during this 9-week followup at 3, 6, and 9 weeks. In contrast to the blinded administration of rTMS, all patients during the follow-up period were

administered active citalopram but were not aware of whether they had received active or sham rTMS.

Statistical analysis

Statistical analysis was performed using simple chi-squared analysis or Fisher exact test as appropriate for categorical variables. Because some of our continuous measures were not normally distributed, the Wilcoxon rank sum test was used to compare continuous variables between the active and sham groups. We used the Kruskal-Wallis test for comparing the active responders with the active nonresponders and sham groups.

Results

The background characteristics and assessment before starting citalopram are shown in Table 1. There were 13 patients who responded to rTMS treatment during the 3 weeks of rTMS stimulation, while 20 patients who received active treatment showed no treatment response. Among the patients who received sham treatment, 2 patients responded while 27 patients failed to respond. Although the patients who responded to sham treatment were too few to analyze, the background characteristics of the patients who responded to treatment with active rTMS, those who failed to respond to treatment with active rTMS, and those who failed to respond to sham treatment are shown in Table 2. There were no statistically significant differences in background or impairment measures between responders and non-responders. There were no significant differences in the FIM [mean (SD)], MMSE [mean (SD)] background characteristics or previous depressive episodes among the three groups. (Table 2).

rTMS responders

Of the 13 patients who responded to rTMS treatment, 4 patients (30.8%) relapsed during the 9 weeks of administration of citalopram, 3 developed major depression and 1 minor depression. The mean HDRS-17 scores for the patients who did not relapse over the 9 week course of continuation treatment showed continued improvement (Figure 1). There were no significant differences between patients who relapsed and those who did not relapse in age, gender, education, or prior exposure to citalopram (i.e. 1 of 4 patients who relapsed and 1 of 9 who continued to respond had previous exposure to citalopram (Fishers exact $p=0.46$ [2-tailed])). Furthermore, 2 of the 4 patients who relapsed had more than 3 prior episodes of depression compared to only 1 of 9 who did not relapse (Fisher's exact $p=0.20$). Imaging analysis found that left frontal grey matter volume was almost identical in the relapsers and non-relapsers (i.e. 115.8 ± 14.9 SD vs 115.1 ± 13.2 SD), however, left frontal white matter hyperintensity volume was 5.1 ± 8.0 SD for relapsers and 1.4 ± 1.9 SD for non-relapsers (ANCOVA adjusted for total brain volume ($F_{1,11}=1.21$, $p=.45$)).

Non responders

There were 20 patients who received active rTMS who failed to respond to this treatment and 27 patients who received sham stimulation who also failed to respond. Among the 27 sham nonresponders, 4 responded to treatment by week 9 (i.e. 14.8% response rate). Among the patients receiving active rTMS, 5 of 20 nonresponders responded during the 9 weeks of treatment with escitalopram (i.e. 25% response rate) (Figure 2).

Discussion

This preliminary study, for the first time, examined continuation treatment with citalopram following response of vascular depression to treatment with rTMS. Of 13 responders, 9 improved during continuation treatment and 4 relapsed (3 major depressions, 1 minor

depression). Of the 45 non-responders, a total of 9 patients responded during 9 additional weeks of continuation treatment.

Before discussing the implications of these findings, the limitations of the study should be acknowledged. First, the study was non-blinded. We had insufficient numbers of responders to assess relapse comparing citalopram continuation with placebo. Thus, all patients received active citalopram. Second, only 13 patients responded to treatment and thus, our conclusions from this non-blinded maintenance trial are preliminary estimates. Third, we did not increase the dose of citalopram above 20 mg because, although this failure to increase the citalopram dose may have contributed to the relapse rate or failure of response, we felt that trying to increase the dose would complicate the interpretation of findings even more. Finally, only half of our patients in the original study had MRI-defined vascular depression. Thus, whether these patients would be more or less responsive to citalopram maintenance is uncertain. In the rTMS protocol, however, we found no difference in treatment response among MRI or clinically defined vascular depression (7).

Given these limitations, how might the findings from this study be construed? Our major finding was a rather disappointing relapse rate of 4 of 13 patients occurring within 9 weeks after response to rTMS. This estimate of relapse (i.e. approximately 30%), however, is similar to the findings of Reynolds et al. (15). Among elderly patients who responded to treatment of depression, 14 of 63 patients (22.2%) receiving paroxetine relapsed during the first 9 weeks of maintenance treatment. These findings are also consistent with previous reports of 50 to 90% recurrence rates over 2 to 3 years among elderly patients with a history of depression (16,17).

Our study, however, is perhaps most similar to maintenance trials following electroconvulsive therapy (ECT). During 24 weeks of continuation treatment following remission on ECT, Sackheim et al. (18) found that 84% of patients on placebo, 60% on nortriptyline and 39% on antidepressant + lithium relapsed. Kellner et al. (19) found that ECT and pharmacologic therapy following remission of major depression treated with ECT, had similar relapse rates (i.e. 37.1% for ECT and 31.6% for combination of nortriptyline and lithium) (19). Thus, relapse rates are high in both elderly and younger patient populations and more effective continuation and maintenance therapies need to be developed.

Although prior research has documented the high rates of relapse and recurrence among elderly depressed patients, the risk factors for rapid relapse following treatment response are relatively few. Our findings that 2 of 4 relapse patients, while only 1 of 9 non-relapse patients, had 3 or more prior episodes of depression and secondly, that relapse patients had 3.6 times large volumes of left frontal white matter hyperintensities than non-relapse patients suggests these may be important risk factors for relapse following rTMS. Future research might confirm these risk factors for relapse after rTMS treatment as well as identifying other risk factors for rapid relapse.

In conclusion, this continuation trial of citalopram following treatment of vascular depression using rTMS, is the first study to examine this important clinical issue. During a 9 week course of treatment with citalopram 30.8% of responders relapsed. Increased numbers of prior depressions and greater volume of vascular ischemia in the left frontal white matter may contribute to increased vulnerability to relapse. Further studies of techniques for continuation and maintenance are clearly needed.

Acknowledgments

The authors want to thank Stephanie Rosazza and Teresa Kopel and Albert Abreu for their help with patient evaluation, rTMS administration and follow-up assessments. This study was funded by NIH grant R01 MH 063405.

This work was supported in part by NIMH grants R01 MH-63405 and R01 MH065134.

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Figure 1. Responders to rTMS

Hamilton 17-item depression scores (mean $\pm$ SD) for patients who responded to treatment with rTMS during the initial to 3 week period. From 3 to 12 weeks, patients were divided into those who relapsed, defined as meeting DSM-IV criteria for major or minor depression, with at least a 4 point increase in their HamD-17 score and those who did not relapse. Note that the relapsers did not have a “partial” response to rTMS and that the non-relapsers showed improvement (consolidation) with continued antidepressant treatment.

Figure 2. 9 weeks of citalopram after rTMS

The percent of patients who had a greater than 50% decline in Hamilton 17-item depression scores during 9 weeks of treatment with citalopram. Of the 13 patients who had responded to rTMS treatment, 4 of 13 were no longer responders after 9 weeks of citalopram, while 9 of 43 patients (20.9%) who failed to respond did respond to citalopram.

Table 1**Background Characteristics**

Characteristics	TCD-18K N=33	Sham N= 29	Statistical analysis
Age [yrs, mean (SD)]	64.5 (8.9)	63.3 (8.6)	$\chi^2_{(1)} = 0.168, p = 0.6820$
Sex [% female]	20 (61)	17 (59)	$\chi^2_{(1)} = 0.025, p = 0.8737$
Marital status [% married]	25 (76)	20 (69)	$\chi^2_{(1)} = 0.098, p = 0.7544$
Education [yrs, mean (SD)]	14.5 (2.5)	14.3 (2.1)	$\chi^2_{(1)} = 0.076, p = 0.7829$
SES [% classes IV-V]	9 (27)	6 (21)	$\chi^2_{(1)} = 0.094, p = 0.7590$
Medical comorbidity			
Cumulative illness rating scale score [mean (SD)]	1.7 (0.4)	1.1 (0.3)	$\chi^2_{(1)} = 0.321, p = 0.5711$
No of cardiovascular risk factors [mean (SD)]	2.5 (1.0)	2.6 (0.8)	$\chi^2_{(1)} = 0.805, p = 0.3695$
Functional Independence Measure score [mean (SD)]	66.7 (5.4)	66.8 (4.8)	$\chi^2_{(1)} = 0.001, p = 0.9830$
Major dep, No. (%) of patients	28 (85)	22(77)	$\chi^2_{(1)} = 0.327, p = 0.5677$
HAMD-17 score baseline [mean (SD)]	18.7 (2.9)	17.6 (4.6)	$\chi^2_{(1)} = 1.467, p = 0.2258$
Recurrence, No (%) of patients with > 3 episodes	12 (36)	13 (45)	$\chi^2_{(1)} = 0.175, p = 0.6756$

Wilcoxon rank sum test was used for continuous variables.

Chi square test or Fisher exact test was used for categorical variables.

Table 2
Background characteristics and course of depression

Characteristics	Sham – non-responders N=27	Active non-responders N=20	Active responders N=13	Statistical Analysis
Age [yrs, mean (SD)]	63.8 (8.7)	64.9 (9.7)	63.8 (7.8)	$\chi^2_{(2)} = 0.094, p = 0.9541$
Sex [% female]	17 (62.9)	11(55)	9 (69.2)	$\chi^2_{(2)} = 0.710, p = 0.7010$
Education [yrs, mean (SD)]	14.1 (2.0)	14.1 (2.6)	15.1 (2.1)	$\chi^2_{(2)} = 2.372, p = 0.3055$
Functional Independence Measure score [mean (SD)]	66.5 (4.9)	65.9 (6.1)	68.0 (3.8)	$\chi^2_{(2)} = 1.252, p = 0.5347$
MMSE [mean (SD)]	28.3 (1.8)	28.1 (1.3)	28.9 (1.3)	$\chi^2_{(2)} = 3.741, p = 0.1540$
Patients with > 3 episodes of prior dep [%]	12 (44.4)	9 (4.5)	3(23.1)	$\chi^2_{(2)} = 1.980, p = 0.3710$

Kruskal Wallis test was used for continuous variables.

Chi square test or Fisher exact test was used for categorical variables.