Progress in Neuro-Psychopharmacology & Biological Psychiatry 34 (2010) 1446–1449

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Pramipexole for stage 2 treatment-resistant major depression: An open study

Takeshi Inoue *, Yuji Kitaichi, Takuya Masui, Shin Nakagawa, Shuken Boku, Teruaki Tanaka, Katsuji Suzuki, Yasuya Nakato, Reiko Usui, Tsukasa Koyama

Department of Psychiatry, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan

ARTICLE INFO

Article history:
Received 9 March 2010
Received in revised form 30 June 2010
Accepted 31 July 2010
Available online 11 August 2010

Keywords:
Augmentation therapy
Dopamine receptor agonist
Mood disorder
Pramipexole
Treatment-resistant depression

ABSTRACT

Objective: To examine the effectiveness and safety of adjunctive pramipexole in the treatment of stage 2 treatment-resistant major depressive disorder.
Methods: This study included patients with moderate or non-psychotic severe major depressive disorder according to DSM-IV-TR criteria despite at least two adequate treatment trials with antidepressants from different pharmacological classes. Pramipexole 0.25 to 2 mg daily was added to antidepressant therapy. Previous treatments were continued unchanged, but no new treatments were allowed. We conducted assessments at baseline and at weeks 2, 4, 6, and 8. We defined response as a 50% or greater reduction on the Montgomery–Åsberg Depression Rating Scale (MADRS).
Results: Ten patients (4 men, 6 women) aged 43.7 ± 11.4 years received pramipexole at mean dose of 1.3 ± 0.6 mg/d. Mean MADRS scores improved significantly from baseline to endpoint (mean differences = 11.4, 95% CI [4.1, 18.7], $P = 0.0064$). At the endpoint, six of 10 (60%) were responders on MADRS (≥50% reduction). Two patients (20%) terminated early due to mild somatic and psychiatric adverse effects.
Conclusion: These preliminary data suggest that the addition of pramipexole to antidepressant treatment may be effective and well tolerated in patients with stage 2 treatment-resistant major depressive disorder.

1. Introduction

Treatment-resistant major depression is a major issue in clinical practice, and the search for new, more effective treatments is ongoing. In general, treatment-resistant major depression is defined as the persistence of significant or moderate depressive symptoms despite at least two treatment trials with antidepressants from different pharmacological classes [stage 2 major depression according to the staging of depression based on prior treatment response proposed by Thase and Rush (1995)]. Each prior treatment must have been used in an adequate dose for an adequate period (i.e., a minimum of the equivalent of 150 mg of imipramine for 4 weeks) (Thase and Rush, 1995). The prevalence of treatment-resistant major depression is estimated to be 5–10% among all patients with major depression (Inoue et al., 2002). Nevertheless, most studies have investigated non-responders to single antidepressant trials [stage 1 major depression by Thase and Rush (1995)] and defined these patients as having treatment-resistant major depression (Thase and Rush, 1995). Furthermore, because of short treatment periods and small doses of antidepressants in several studies, there has been little evidence regarding effective therapy for stage 2 treatment-resistant major depression (Stimpson et al., 2002). Electroconvulsive therapy, lithium augmentation, and thyroid augmentation are recommended as treatment options in the World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Unipolar Depressive Disorders (Bauer et al., 2002), and have some evidence for stage 1 depression, but unexpectedly, little evidence for stage 2 treatment-resistant major depression has been noted (Stimpson et al., 2002). It is noteworthy that growing evidence for the treatment of stage 2 treatment-resistant major depression has shown clinical efficacy for atypical antipsychotic drugs (olanzapine and aripiprazole) as adjunctive therapy in large-scale randomized clinical trials (Thase et al., 2007; Marcus et al., 2008). Moreover, adjunctive repetitive transcranial magnetic stimulation was shown to be effective for stage 2 major depression in a small randomized clinical trial (Fitzgerald et al., 2006), whereas monotherapy with repetitive transcranial magnetic stimulation has been proven effective only for stage 1 major depression (O'Reardon et al., 2007).

A growing number of studies report abnormalities in the dopaminergic system in major depression, and the efficacy of pro-dopaminergic drugs, including dopamine receptor agonists, for major depression have been reported (Papakostas, 2006). The idea that major depression resistant to treatment with multiple serotonergic- and noradrenergic-based antidepressants may be responsive to pro-dopaminergic drugs is rational in terms of the mechanism of action of

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning; HDRS, Hamilton Depression Rating Scale; LOCF, last-observation-carried forward; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; DSM-IV-TR, Diagnostic and statistical manual of mental disorders, 4th edition, text revision.

* Corresponding author. Department of Psychiatry, Neural Function, Hokkaido University Graduate School of Medicine, North 15, West 7, Sapporo 060-8638, Japan. Tel.: +81 11 706 5160; fax: +81 11 706 5081.
E-mail address: tinoue@med.hokudai.ac.jp (T. Inoue).

0278-5846/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2010.07.035

these drugs. Several studies have reported that dopamine receptor agonists (bromocriptine, pergolide, pramipexole, and ropinirole) are effective for stage 1 major depression that fails to respond to at least a single adequate conventional antidepressant treatment trial (Inoue et al., 1996; Izumi et al., 2000; Sporn et al., 2000; Lattanzi et al., 2002; Cassano et al., 2005). As mentioned above, the clinical efficacy of dopamine receptor agonists for stage 2 treatment-resistant major depression has not been assessed.

This pilot prospective, open study was undertaken to investigate the efficacy and safety of pramipexole in patients with stage 2 treatment-resistant major depression.

2. Methods

2.1. Subjects

We conducted an 8-week, open-label trial of pramipexole for patients with stage 2 treatment-resistant major depression at the Department of Psychiatry, Hokkaido University Hospital, Sapporo, Japan. The inclusion period started in June 2005 and ended in October 2008.

We included patients of both sexes, aged 20 to 70 years, with a diagnosis of moderate or non-psychotic severe major depressive disorder according to DSM-IV-TR criteria despite at least two treatment trials with antidepressants from different pharmacological classes, each used in an adequate dose for an adequate time period (i.e., a minimum of the equivalent of 150 mg of imipramine for 4 weeks) (Thase and Rush, 1995). Patients with scores of 20 or greater on the Montgomery–Åsberg Depression Rating Scale (MADRS, 10 items) (Montgomery and Åsberg, 1979) or scores of 60 or less on the Global Assessment of Functioning (GAF) Scale (even if MADRS scores were less than 20) were included. Patients with organic brain syndrome, schizophrenia, bipolar or schizoaffective disorder, severe physical illness, a history of substance use, or marked suicidality were excluded. All subjects provided written informed consent, and the trial was approved by the institutional review board of Hokkaido University Graduate School of Medicine.

2.2. Intervention and measurements

Subjects entering this study were prescribed pramipexole. All took one or two antidepressants, and doses of these drugs were held constant throughout the study. Pramipexole administration was started at 0.125 mg twice daily and increased 0.25–0.5 mg/day every 7 days to a target range of 0.5–2 mg/day. Higher doses (up to 3 mg/day) were permitted as needed. Dose escalations continued until 1) achievement of the primary endpoint (defined as a reduction of 50% or more from baseline in MADRS score), 2) drug intolerance, or 3) the 8-week protocol completion. Dosages were adjusted individually for patients.

Clinical assessments of adverse events and drug compliance were performed at each visit (every day for three inpatients) by trained psychiatrists at baseline and weeks 2, 4, 6, and 8. Outcomes were assessed using the MADRS score, the 17-item Hamilton Depression Rating Scale (HDRS) (Williams, 1988), and the GAF scale. The primary efficacy measure was the MADRS score. Secondary efficacy measures were the 17-item HDRS and GAF scores. Spontaneously reported adverse events were recorded at each visit.

2.3. Data analysis

All analyses were carried out on an intent-to-treat basis. Longitudinal efficacy outcomes (MADRS, HDRS, and GAF) were analyzed using paired *t*-tests comparing baseline and last-observation-carried forward (LOCF) results, with α set at 0.05; all tests were 2-tailed.

The primary outcome was defined as treatment response based on a ≥50% reduction in MADRS score over 8 weeks using LOCF methodology. Remission was defined as MADRS score<10 at the last visit (LOCF).

Secondary outcomes were determined using HDRS and GAF scores. Secondary treatment response was defined as a ≥50% reduction in HDRS score or a 10-point improvement (increase) in GAF score. Functional recovery was defined as GAF score>70 (Haykal and Akiskal, 1999; Furukawa et al., 2001). Changes in scores from baseline to final study visit were calculated for the MADRS, HDRS, and GAF. Pearson's correlation coefficients between GAF changes and MADRS or HDRS changes were calculated to assess potential predictors of functional improvement.

All continuous data are presented as means with standard deviations or 95% confidence intervals (CIs).

3. Results

Clinical and demographic characteristics of subjects are shown in Tables 1 and 2. All patients were diagnosed with non-psychotic major depressive disorder, moderate ($n=9$) or severe ($n=1$) with melancholic features. The mean peak dose of pramipexole was 1.3 mg/day (SD = 0.6). Eight of 10 patients (80%) completed the 8-week trial. Two patients discontinued the trial due to lack of efficacy and adverse events. As shown in Table 2, all 10 patients took one or two concurrent antidepressants.

Six of 10 patients (60%) were judged to be treatment responders based on the MADRS (≥50% reduction). Among the 10 patients, MADRS scores improved statistically significantly from baseline to the primary endpoint (mean difference = 11.4, 95% CI [4.1, 18.7], $P=0.0064$). Six patients achieved a MADRS score<10 at last visit (LOCF), yielding a 60% remission rate. As seen in Fig. 1A, this improvement was seen in week 2 and remained statistically significant throughout the study and at endpoint (LOCF). Eight items on the MADRS showed significant mean changes from baseline to endpoint (LOCF): apparent sadness, 1.90 (95% CI 0.92, 2.88), $P=0.0018$; reported sadness, 1.30 (95% CI 0.47, 2.13), $P=0.0063$; inner tension, 1.30 (95% CI 0.40, 2.20), $P=0.0095$; reduced sleep, 1.40

Table 1
Baseline characteristics of 10 patients with major depressive disorder.

Characteristic	Value
Diagnosis	
Major depressive disorder, single episode, *n* (%)	6 (60)
Major depressive disorder, recurrent, *n* (%)	4 (40)
Sex	
Female, *n* (%); male, *n* (%)	4 (40); 6 (60)
Age at entry, mean ± SD (yr)	43.7 ± 11.4
Range	29 – 64
Marital status	
Married, *n* (%); single, *n* (%)	7 (70); 3 (30)
Employment status	
Employed, *n* (%); unemployed, *n* (%)	7 (70) ; 3 (30)
Education, mean ± SD (yr)	13.7 ± 2.4
Length of current major depressive episode, mean ± SD (yr)	2.3 ± 1.3
Age at onset of first episode, mean ± SD (yr)	39.6 ± 11.5
Depression episodes, life time, *n* (%)	
1 episode	6 (60)
2 episodes	4 (40)
Patients with failed adequate antidepressant trials, *n* (%)	
2 trials	5 (50)
3 trials	3 (30)
4 trials	1 (10)
5 trials	1 (10)
Baseline MADRS score, mean ± SD	23.9 ± 7.0
Baseline HDRS score, mean ± SD	16.4 ± 4.4
Baseline GAF score, mean ± SD	46.2 ± 8.8

MADRS = Montgomery–Åsberg Depression Rating Scale, HDRS = 17-item Hamilton Depression Rating Scale, GAF = Global Assessment of Functioning.