Personalized medicine in psychiatry xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Personalized medicine in psychiatry

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

Impact of morbid obesity on treatment outcome in a clinical trial of major depressive disorder

Steven D. Targum *, Christopher J. Catania

Bracket Global, 2 Oliver Street, Suite 1003, Boston, MA 02109, United States

ARTICLE INFO

Article history:
Received 21 March 2017
Received in revised form 14 June 2017
Accepted 14 June 2017
Available online xxxx

Keywords:
Body mass index
Depression
Morbid obesity
Moderating factors
Treatment outcome
Antidepressants

ABSTRACT

In a post-hoc analysis, we examined the impact of morbid obesity as measured by body mass index (BMI) on treatment outcome in a small, phase II double blind, placebo-controlled, 6-week, 3-arm study of a combination treatment (buspirone 15 mg with melatonin 3 mg-SR) versus buspirone 15 mg monotherapy or placebo in subjects with Major Depressive Disorder (MDD) experiencing an acute major depressive episode.

Previously, we reported that subjects assigned to the combination treatment did better than subjects assigned to either buspirone monotherapy or placebo on several clinical metrics including the clinical global impression of severity and improvement scales, the Inventory of Depressive Symptomatology (IDSc30), the patient-rated Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}), and the Hamilton rating scale for anxiety.

In this post-hoc analysis, we found that baseline BMI $\geq$ 40 kg/m^2 (WHO definition of morbid obesity) adversely affected signal detection. Post-hoc exclusion of the 22 subjects with baseline BMI $\geq$ 40 from the 123 subjects in the mITT population improved the overall effect size and the statistical significance of the combination treatment over the other two treatment groups on each of the 5 different clinical efficacy assessments.

Morbid obesity often reflects underlying co-morbid conditions and life style differences that may affect the antidepressant treatment response. The findings from this post-hoc analysis suggest that morbid obesity is a moderating factor that may confound the interpretation of clinical trial results by blunting the drug response and/or generating a higher placebo response.

Introduction

Obesity may be a moderating factor that could adversely affect treatment outcome when evaluating novel antidepressants in clinical trials [1–7]. Body weight is often evaluated as body mass index (BMI) defined as weight (kg) divided by the subject's height in meters squared (m^2). Some, but not all clinical studies have reported that subjects with Major Depressive Disorder (MDD) who have a high baseline BMI had a poorer response to antidepressants than subjects with lower baseline BMI [1–3,5,6,8–11]. Metabolic and immunologic differences associated with obesity in contrast to normal weight individuals may contribute to the reported reduced treatment response [12,13]. In a recent meta-analysis, Woo et al. YS [5] summarized these studies and noted that the data was derived from diverse study designs, was often contradictory, and was clearly not conclusive.

We examined the impact of morbid obesity (defined as baseline BMI $\geq$ 40 kg/m^2) on treatment outcome from data obtained in a small, double blind, placebo-controlled study of a combination treatment (buspirone-melatonin) versus buspirone monotherapy or placebo in MDD subjects experiencing an acute major depressive episode.

The combination treatment of buspirone with melatonin was derived from in vitro neurogenesis-based human neural stem cell assays and rodent in vivo behavioral assays conducted by Brain-Cells Inc. [14]. We determined that low dose buspirone 15 mg combined with melatonin-SR 3 mg yielded optimal antidepressant efficacy in the pre-clinical platform whereas neither buspirone nor melatonin alone showed any antidepressant-like profile [14].

In previous papers, we reported that the combination treatment was better than buspirone monotherapy or placebo on 5 different clinical metrics [14,15]. In this post-hoc analysis, we report that

* Corresponding author at: 2 Oliver Street, Suite 1003, Boston, MA 02109, United States.
E-mail address: sdtargum@yahoo.com (S.D. Targum).

http://dx.doi.org/10.1016/j.pmip.2017.06.002
2468-1717/

Please cite this article in press as: Targum SD, Catania CJ. Impact of morbid obesity on treatment outcome in a clinical trial of major depressive disorder. Personalized medicine in psychiatry (2017), http://dx.doi.org/10.1016/j.pmip.2017.06.002

morbid obesity adversely affected signal detection on each of these clinical efficacy assessments.

Material and methods

Data for this analysis were derived from a phase II, 6-week, double-blind, placebo-controlled, randomized trial of a combination treatment (Buspirone 15 mg with melatonin-SR 3 mg) versus buspirone 15 mg monotherapy or placebo in acutely depressed subjects with MDD (CBM-IT-01; BCI NCT 007005003). This combination treatment was studied as a potential antidepressant medication based upon findings from a pre-clinical, neurogenesis-based platform of in vitro and in vivo assays conducted by BrainCells Inc. [14].

142 patients meeting DSM-IV-TR criteria for MDD (confirmed by the Mini International Neuropsychiatric Interview) were enrolled in the study from 9 clinical trial sites located within the United States [14,16,17] of whom 123 subjects received at least one post-randomization assessment and were ultimately evaluable in the modified intent to treat (mITT) population. All subjects gave written documentation of informed consent approved by an institutional review board prior to participation in any study procedures. Eligible subjects required a minimum score of ≥14 on the patient-rated Quick Inventory of Depressive Symptoms 16-item version (QIDS-SR_{16}) at screen and baseline [18]. Subjects were randomly assigned to one of three treatment groups (combination buspirone 15 mg with melatonin 3 mg SR treatment, buspirone 15 mg monotherapy, or placebo) using a 2:1:1 allocation and treated for 6 weeks in a double-blind design. Full details of the study design and results have been published elsewhere [14,15].

Five rating instruments were used to assess efficacy including the clinician-rated Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales, the Inventory of Depressive Symptomatology 30-item version (IDSc30), the Hamilton rating scale for anxiety (Ham-A), and the patient self-rated Quick Inventory of Depressive Symptomatology: QIDS-SR_{16} [18–21].

In this post-hoc analysis, subjects in the mITT population were stratified by their baseline BMI values. The World Health organization (WHO) criteria classify subjects with BMI values <25 kg/m^2 as normal weight for their height, 25 to <30 as overweight, BMI ≥ 30 as obese, and subjects with BMI ≥ 40 as morbidly obese [22].

By design, the planned statistical analyses for this small study included a secondary pooling of the buspirone monotherapy and placebo treatment groups if the final CGI-I values between them were ≤0.04 at endpoint, which they were [14]. Hence, the pooled group was included in all analyses.

Statistical analysis included an analysis of covariance (ANCOVA) using the 6-week endpoint or last observation carried forward (LOCF) value as available, for the CGI-S, IDSc30, QIDS-SR_{16}, and Ham-A, an analysis of variance (ANOVA) for the CGI-I assessments (because there was no baseline contingency measure), and examined the impact of BMI on the calculated effect size (Cohen's d) as well [23]. Treatment response was defined as ≥50% improvement of the total IDSc30 score from the baseline measure at the 6-week study endpoint or the last observation, and remission was defined as a total IDSc30 score ≤11 at endpoint.

Results

The mean baseline BMI for the 123 enrolled subjects was 32.7 ± 8.3 (SD) kg/m^2. The three randomly assigned treatment groups were stratified according to baseline BMI < 30 (normal weight or slightly overweight), BMI ≥ 30 to <40 (obesity), and BMI ≥ 40 (morbid obesity) based upon the WHO standards [22]. Forty-eight of the 123 enrolled subjects (39.0%) had BMI < 30 at the baseline visit, 53 (43.1%) had baseline BMI between 30 and <40, and 22 of the enrolled subjects (17.9%) had baseline BMI ≥ 40 (morbid obesity). Table 1 summarizes the baseline demographic and clinical characteristics of the mITT population and the three randomly assigned treatment groups.

The original study results have been published elsewhere [14]. As shown in Tables 2 and 3, the combination treatment of buspirone 15 mg with melatonin 3 mg-SR achieved statistically significant improvement over the pooled buspirone monotherapy and placebo groups on the CGI-S, CGI-I, IDSc30, and Ham-A after 6-weeks of double-blind treatment, but not on the QIDS-SR_{16} in the mITT population [14].

Impact of morbid obesity on mean change scores of 5 different clinical metrics following 6 weeks of treatment

Table 2 shows the mean change scores from the baseline visit to the 6-week endpoint for the CGI-S, CGI-I, IDSc30, QIDS-SR_{16}, and Ham-A for the mITT population and the different BMI thresholds.

Baseline BMI affected the treatment response on all five clinical metrics. The 50 combination-assigned subjects with baseline BMI < 40 were more responsive to the combination treatment at 6 weeks than the 10 combination-assigned subjects with BMI ≥ 40 on the CGI-S (ANCOVA: F = 2.32; p = 0.130), the IDSc30 (F = 3.38; p = 0.07), the QIDS- SR_{16} (F = 6.3; p = 0.015) and the Ham-A (F = 2.72; p = 0.105).

Post-hoc exclusion of the 22 subjects with morbid obesity revealed an enhanced clinical improvement in the remaining sub population of 101 subjects who had baseline BMI < 40 (Table 3). Each of the five rating instruments revealed a more significant treatment difference favoring the combination treatment over buspirone monotherapy or placebo in the BMI < 40 population relative to the entire mITT population. For instance, the statistical significance of the IDSc30 improved from p = 0.030 to 0.004 for the combination treatment over the pooled buspirone and placebo groups, and the patient self-rated QIDS- SR_{16} improved from p = 0.055 to p = 0.008.

A comparison of the combination treatment subjects versus placebo or buspirone-assigned subjects in the BMI < 40 subpopulation revealed an enhanced effect size (Cohen's d) on all clinical metrics relative to the mITT population (Table 4). Alternatively, the pooled group of subjects with BMI ≥ 40 outperformed the combination treatment.

Treatment outcome in subjects with normal BMI values

In the small sample of subjects (n = 19) who had BMI values <25 kg/m^2 (normal according to WHO standards), the mean total IDSc30 score change from baseline to endpoint was −22.44 ± 11.08 (SD) in 9 combination-treated subjects and only −7.75 ± 18.46 (SD) in 4 placebo-assigned subjects. Similarly, the mean QIDS-SR_{16} score change was −9.89 ± 5.33 (SD) in the 9 combination-treated subjects with baseline BMI < 25 in contrast to only −4.00 ± 8.25 (SD) in the 4 placebo-assigned subjects. However, these small sample sizes were too small for meaningful statistical analyses.

Correlation between baseline BMI and total IDSc30 score changes at 6 weeks

The combination treatment group revealed no significant correlation between each subject's baseline BMI and their total IDSc30 score change at 6-weeks (r = 0.097; t = 0.74; p = 0.231). However, there was a significant correlation between baseline BMI and total IDSc30 score changes at 6 weeks in the pooled buspirone

Please cite this article in press as: Targum SD, Catania CJ. Impact of morbid obesity on treatment outcome in a clinical trial of major depressive disorder. Personalized medicine in psychiatry (2017), http://dx.doi.org/10.1016/j.pmip.2017.06.002