Journal of Affective Disorders 150 (2013) 745–752

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Early improvement as a predictor of acute treatment outcome in manic or mixed episodes in bipolar-1 disorder: A pooled, post hoc analysis from the asenapine development program ☆

Armin Szegedi [a,*], Jun Zhao [a], Roger S. McIntyre [b]

[a] Merck, Rahway, NJ, USA
[b] Mood Disorders Psychopharmacology Unit, University of Toronto, Canada

ARTICLE INFO

Article history:
Received 30 July 2012
Received in revised form
22 January 2013
Accepted 28 January 2013
Available online 6 March 2013

Keywords:
Bipolar mania
Antipsychotics
Early improvement
YMRS
CGI–BP

ABSTRACT

Objective: To assess whether early symptom improvement predicts later treatment outcome in acute manic/mixed episodes of bipolar I disorder using Young Mania Rating Scale (YMRS) or Clinical Global Impression scale, bipolar disorders (CGI–BP) assessments.
Methods: Data were pooled from two 3-week randomized controlled studies with asenapine (ASE; $n=372$), olanzapine (OLA; $n=391$), or placebo (PL; $n=197$). Early improvement was defined as reduction of YMRS total scores ($\geq 15\%$, $\geq 20\%$, $\geq 25\%$) or CGI–BP severity scores (≥ 1 point change) at days 2, 4, and 7. Treatment outcome at week 3 was defined as response (YMRS: $\geq 50\%$ score reduction; CGI–BP severity: "minimally ill" or better) or remission (YMRS total score ≤ 12; CGI–BP severity: "not at all ill"). Odds ratios (ORs) and predictive performance statistics were calculated.
Results: Early improvement occurred in a substantial percentage of patients and was associated with significantly increased ORs for response or remission. For ASE, results were significant as early as day 2 on all measures of YMRS and CGI-severity of mania assessment. For all treatments sensitivity and negative predictive values increased from days 2 to 7 for all YMRS and CGI–BP measures, while specificity values decreased.
Conclusion: In acute manic/mixed episodes, early improvement within 1 week of treatment was associated with significantly increased ORs of endpoint response or remission. While only a subset of early improvers reach the endpoint treatment goals, absence of improvement within week 1 of treatment initiation strongly predicts the unlikely success of subsequent treatment. Further, CGI-based predictors had predictive properties similar to those based on the YMRS scale.

1. Introduction

Contrary to earlier assumptions of a "delayed onset" of antipsychotic drugs in the treatment of schizophrenia, more recent data from meta-analyses of randomized controlled studies in schizophrenia showed that a substantial proportion of patients develop clinically relevant improvement early in the course of treatment (Agid et al., 2003; Kapur et al., 2005; Leucht et al., 2005). The absence of early improvement in schizophrenia was reported to strongly predict subsequent nonresponse with continued treatment (Kinon et al., 2008; Leucht et al., 2007). More recently, it was reported in a prospective study that patients showing early improvement with risperidone (RIS; initial treatment) at 2 weeks showed greater symptom reduction at endpoint, whereas early nonimprovers, randomized after 2 weeks to either continue with RIS or switch to olanzapine (OLA) for an additional 10 weeks, showed less symptom reduction than was observed with early improvers (Kinon et al., 2010). The results from this study and earlier reports (Kinon et al., 2008; Leucht et al., 2007) clearly demonstrate that early improvement has substantial clinical value as a predictor of treatment outcome in schizophrenia.

Early improvement with different types of antidepressants has also been shown to have predictive value for treatment decisions in major depression (Szegedi et al., 2009). In bipolar depression, the predictive value of early nonimprovement for subsequent nonresponse has been reported in a database of large randomized clinical trials (Kemp et al., 2011a). In the treatment of acute manic episodes Kemp and colleagues have reported that early improvement after 1 week of treatment with OLA or RIS was a good predictor of treatment response (Kemp et al., 2011b; Ketter et al., 2010). Since rapid symptomatic improvement is a key goal, particularly in the treatment of acute mania with mixed episodes (Ketter et al., 2010),

☆ Previous presentation: Part of the data was presented at the ACNP conference, December 4–8, 2011, Waikoloa, HI.

* Correspondence to: Tel.: +732 594 5825; fax: +732 594 5770.
E-mail address: armin.szegedi@merck.com (A. Szegedi).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.01.024

identifying the likely nonresponders as early as possible has substantial importance for successful management.

We therefore performed a pooled post hoc analysis on datasets of two 3-week randomized controlled trials conducted in patients with manic or mixed episodes associated with bipolar I disorder treated with asenapine (ASE), OLA, or placebo (PL). Asenapine is an antipsychotic agent indicated in the United States for treatment of adults with schizophrenia and as monotherapy or adjunctive therapy with lithium or valproate in the treatment of manic or mixed episodes associated with bipolar I disorder and in the European Union for the treatment of moderate to severe manic episodes associated with bipolar I disorder. Primary results from these two randomized controlled studies have been reported previously (McIntyre et al., 2009, 2010). In this analysis we aimed to evaluate whether early improvement (assessed with the Young Mania Rating Scale (YMRS) and Clinical Global Impression (CGI) scale), that occurs in an individual patient within the first week of treatment, has predictive value on individual treatment outcome.

2. Methods

2.1. Study design

A post hoc analysis was performed on pooled data from two multinational, 3-week, phase 3 studies that compared flexible dose ASE and OLA with PL in patients with bipolar I disorder (www.clinicaltrials.gov identifier: NCT00159744; NCT00159796) (McIntyre et al., 2009, 2010). Briefly, the trials included adult patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for primary diagnosis of manic or mixed episodes of bipolar I disorder. The well-established YMRS was used by the treating clinicians to assess the severity of manic symptoms. The overall symptom severity was assessed using the CGI version for bipolar disorders (CGI–BP), assessing severity of mania and overall illness. Patients were required to have a total score ≥ 20 on the YMRS scale at screening and baseline, a current bipolar I episode that began ≤ 3 months before screening, and documented history of >1 moderate to severe mood episode with or without psychotic features. Individuals with a psychotic disorder or primary diagnosis other than bipolar I disorder or patients who experienced rapid-cycling bipolar disorder during the past year were excluded.

2.2. Treatment

Patients were randomized to 3 weeks of double-blind, sublingual ASE (10 mg twice daily on day 1, flexible dose of 5–10 mg twice daily thereafter), PL, or OLA (15 mg on day 1, flexible dose of 5–20 mg every day thereafter) in a ratio of 2:1:2 (McIntyre et al., 2009, 2010).

2.3. Outcome measures

The following efficacy outcome measures were prespecified in the clinical trial protocols:

- The primary efficacy endpoint was change in YMRS total score from baseline to day 21.
- Secondary efficacy endpoints included change from baseline in bipolar severity of mania and overall illness in CGI–BP rating scales, and the percentage of YMRS responders (patients demonstrating $\geq 50\%$ YMRS total score reductions at endpoint), and YMRS remitters (patients with YMRS total scores ≤ 12 at endpoint).

Assessments using YMRS and CGI–BP were conducted at screening, baseline, and on treatment days 2, 4, 7, 14, 21, or at study endpoint (McIntyre et al., 2009, 2010).

For the purpose of this post hoc analysis, the following patient groups were defined:

Using YMRS total score:

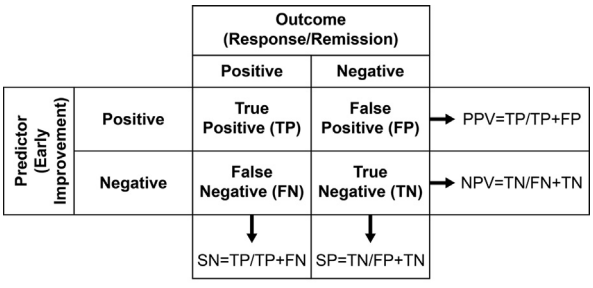
1. Early improvers: a reduction from baseline in total score $\geq 15\%$, $\geq 20\%$, $\geq 25\%$ (cut-off points) assessed at visit days 2, 4, and 7.
2. Treatment responders: a reduction from baseline in total score $\geq 50\%$ at week 3.
3. Treatment remitters: a reduction from baseline in total scores ≤ 12 at week 3.

Using CGI–BP severity of mania or overall illness scores:

1. Early improvers: a reduction from baseline CGI–BP severity score (baseline ≥ 4, either mania or overall illness) by at least one point assessed at visit days 2, 4, and 7.
2. Treatment responders: a CGI–BP severity score (either mania or overall illness) of "minimally ill" or better at week 3.
3. Treatment remitters: a CGI–BP severity score (either mania or overall illness) of "not at all ill" at week 3.

2.4. Statistical analyses

Predictive value of early improvement for later response or remission was performed at week 3 on the intent-to-treat (ITT) population. Patients with missing values or missing early improvement were not included in the analyses and those with missing week 3 data were considered as nonresponders or nonremitters for the purpose of this analysis. The number of early improvers, responders, or remitters assessed using YMRS and CGI–BP severity of mania/CGI–BP severity of overall illness scores were entered into a contingency table and the associations between early improvement (visit days 2, 4, 7) and treatment response or remission at week 3 were assessed using odds ratios [OR] with 95% CI. The p-values were calculated using Fisher's exact test. The predictive performance statistics, which included the following [Fig. 1], were calculated for each treatment group using the early response cut-off values (Kemp et al., 2011b; Szegedi et al., 2009).



PPV, positive predictive value; NPV, negative predictive value; SN, sensitivity; SP, specificity.

Fig. 1. A schematic overview of predictive performance variables and their relationship to early improvement and treatment outcome.