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Research paper

Effect of agomelatine 25–50 mg on functional outcomes in patients with major depressive disorder

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ABSTRACT

Purpose: The purpose of this work is to investigate the effect of agomelatine on functioning compared with placebo in patients suffering from Major Depressive Disorder (MDD).
Methods: Data from two randomized, parallel, double-blind, placebo-controlled short-term agomelatine trials conducted by the manufacturer, one in adult and one in older patients, that evaluated the effect on social functioning, were pooled. The short term effect of agomelatine on social functioning was assessed using the Sheehan Disability Scale (SDS), according to SDS total and sub-item scores, as well as on functional response and remission rates. The Hamilton Depression rating scale was used to quantify severity of depression symptoms. A meta-analytic method using a random effect model was used to assess differences in treatment.
Results: In total, 633 patients (422 on agomelatine; 211 on placebo) were included in the analyses. At endpoint, there was a significant difference in favor of agomelatine *vs* placebo of 3.47 (0.62) (95% confidence interval: [2.26; 4.67]; $P < 0.001$) on the SDS total score. Rates of symptomatic response and remission according to HAM-D_{17} total score were significantly higher in patients taking agomelatine (54.3% and 18.3% respectively) than in those taking placebo (29.4% and 9.5% respectively) with respective differences of 24.9%, $p < 0.001$ and 9.3%, $p < 0.001$. The functional response rates were 52.9% on agomelatine and 34.5% on placebo, with a significant placebo-agomelatine difference in favor of agomelatine of 18.30 ± 4.39% (95% CI: [9.69; 26.91], $p < 0.001$). The functional remission rates were 22.3% with agomelatine and 10.2% with placebo, with a significant difference in favor of agomelatine of 11.7 ± 3.11% (95% CI: [5.61; 17.79], $p < 0.001$). Combined symptomatic and functional response rates were 42.1% on agomelatine and 23.2% on placebo ($p < 0.001$), and the combined symptomatic and functional remission rates were 13.9% on agomelatine and 6.8% on placebo ($p < 0.005$).
Conclusion: This study confirms the efficacy of agomelatine in improving social functioning in MDD patients.

1. Introduction

The mechanism of action of agomelatine, a 5HT2c antagonist and melatonergic agonist, differs from that of other currently approved medications for major depressive disorder (MDD) (Guardiola-Lemaitre et al., 2014). A number of trials have demonstrated the antidepressant efficacy of agomelatine relative to placebo in adults (Demyttenaere et al., 2013; Kennedy and Rizvi, 2010; Kennedy et al., 2014) and elderly (Heun et al., 2013), and to other antidepressants (Demyttenaere et al., 2013). In general, agomelatine has a high level of acceptability and efficacy (Cipriani et al., 2018), but its impact on function has not been systematically evaluated.

Depression is the leading cause of disability world-wide (GBD 2016 DALYs and HALE Collaborators 2017) with approximately 50% of costs being attributable to workplace costs (World Health Organization, 2018). Traditionally, long-term efficacy assessments commonly focus on symptom-based remission instead of complete symptomatic recovery (Fava et al., 2007; Judd et al., 2000). With growing recognition of the importance of social functional recovery in depressed patients (Habert et al., 2016; Lee et al., 2018) measures of functional outcomes should be included in the evaluation of therapeutic efficacy (Heun et al., 2013; Kennedy et al., 2014; Mancini et al., 2012; Asnis et al., 2013; Lam et al.,

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2014; Montgomery et al., 2014; Briley and Moret, 2010; Soares et al., 2009). This is particularly relevant in aging patients with depression where co-morbid medical disorders are frequently associated with poor functional outcomes (Niti et al., 2007). By assessing the level of functioning in addition to depressive symptoms, one likely achieves a more complete picture of "real-world" outcomes of depressed patients (Langlieb and Guico-Pabia, 2010).

The effects of pharmacological treatment on work/school, social life, and family/home functioning can be assessed using the self-rated Sheehan Disability Scale (SDS) (Sheehan et al., 1996). Here we report on a pooled analysis from two randomized placebo-controlled agomelatine 25–50 mg/day clinical studies conducted by the manufacturer that used the SDS to measure social functioning. The primary symptomatic outcome results of those studies have been published (Heun et al., 2013; Kennedy et al., 2014). This analysis aims to describe the short-term impact on social functioning as measured by the SDS in adult and older (≥65 years old) MDD patients who were treated for up to 8 weeks with agomelatine compared to placebo.

2. Materials and methods

2.1. Data sets

Analyses were based on data from the two randomized, parallel, double-blind, placebo-controlled agomelatine efficacy trials conducted by the manufacturer, where functionality was also evaluated using the SDS in adult patients between 18 and 65 years inclusive and with three agomelatine arms (agomelatine 10 mg, agomelatine 25 mg fixed and agomelatine 25–50 mg) (study 1) and in older patients aged at least 65 who received agomelatine in a flexible dosing protocol (agomelatine 25–50 mg) (study 2). In study 1, 133 patients were randomised to receive agomelatine 10 mg (not included in this analysis), 138 to agomelatine 25 mg (fixed dose), 137 to agomelatine 25–50 mg (flexible dose), and 141 to the placebo arm. In the second study, 151 patients were randomised to receive agomelatine and 71 to receive placebo. All patients met criteria for a moderate to severe Major Depressive Episode and a primary diagnosis of MDD according to DSM-IV-TR (American Psychiatric Association, 2000). Both studies involved an acute treatment phase of at least 6 weeks, and used the score on the Sheehan Disability Scale (SDS) as a secondary endpoint to assess the functional impact of treatment. Studies were approved by local Ethical Review Boards and were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

For the purpose of this pooled analysis, only patients treated with placebo or agomelatine at approved therapeutic doses of either 25 mg/day or 25–50 mg/day were considered. In the 6 week-study 1, a fixed dosage (25 mg/day) and a flexible dosage with up-titration in case of insufficient improvement at week 2, according to a predefined dose adjustment algorithm (25–50 mg/day), were assessed. In study 2, which lasted 8 weeks, patients initially received agomelatine 25 mg, and this dose could be uptitrated to 50 mg daily after 2 weeks, if there was insufficient improvement (using a predefined dose adjustment algorithm). No additional pharmacotherapy or psychotherapy was permitted (except for Argentinean patients in study 1, if antidepressants listed as forbidden were being administered to a patient prior to the study and were effective [or administered less than 4 weeks before the selection]). Both investigators and subjects were blind to the uptitration. Analyses were carried out using data at the short-term endpoint (6–8 weeks after baseline).

2.2. Scales and assessments

Social functioning was assessed using the self-rated SDS (Sheehan et al., 1996), which measures the impact of depression on work/school, social life, and family life/home responsibilities. The SDS total score is the sum of the three domain scores and may range from 0 to 30. A total score of 12 or less is considered a 'functional response', while a total score of 6 or less is a good indicator of 'functional remission' (Sheehan and Sheehan, 2008). For study 1, patients who indicated they were not working or studying during the trial for reasons unrelated to depression did not complete the work score and so were excluded from the analysis on the work score and on the total score.

Antidepressant efficacy over 6–8 weeks was assessed using the last post-baseline value on the total score on the HAM-D_{17} scale; symptomatic response (at least 50% decrease from baseline on the HAM-D total score), symptomatic remission (HAM-D total score lower than or equal to 7), and the HAM-D 'core subscore' (Bech et al., 2009) that was based on the summation of scores on six items: (item 1: depressed mood; item 2: feeling guilt; item 7: work and activities; item 8: retardation; item 10: anxiety psychic; item 13: general somatic symptoms) were all secondary endpoints.

To assess 'comprehensive efficacy', concurrent symptomatic and functional response/remission categories were defined according to HAM-D and SDS cut scores.

2.3. Subjects

Eligible patients were required to score ≥22 on HAM-D_{17}, ≥4 on item 1 of the Clinical Global Impression (CGI) scale (Guy, 1976); and ≥11 on the Hospital Anxiety and Depression Scale (HADS) depression subscale (Zigmond and Snaith, 1983). In study 2 older patients were also required to score ≥27 on the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and to complete the Geriatric Depression Scale (GDS) (Yesavage, 1988). Patients with a decrease of greater than 20% on the HAM-D_{17} scale between selection and inclusion were excluded. All patients were required to be physically healthy or to have stabilized somatic illnesses. Exclusion criteria have been described previously (Heun et al., 2013; Kennedy et al., 2014).

2.4. Statistical analyses

Statistical analyses were performed in the Full Analysis Set (FAS, randomized patients who took at least one dose of medication, with ratings at baseline and at least one post-baseline visit for the primary efficacy criterion). Missing data were imputed with the Last Observation Carried Forward approach for all post-baseline criteria.

In both studies, the agomelatine treatment group was compared to the placebo group over the 6-8-week period in the FAS for SDS work/daily activities, social life and family life scores, and total score, taking into account the mean last post-baseline value using a two-sided Student's *t*-test for independent samples. A meta-analytic method was employed to estimate the overall treatment effect using a random effect model. The same meta-analytic methods assessed agomelatine-placebo differences on percentages of patients with functional response and/or remission taking into account the last post-baseline value over the 6–8 week mandatory period.

Agomelatine-placebo differences were examined on the last post-baseline value of the HAM-D_{17} total score over the 6-8-week period, using analysis of covariance with centre and baseline HAM-D_{17} total score as covariates for each study. Results were combined using a meta-analytic method to compute the overall treatment effect using a random effect model in the FAS. An additional unadjusted analysis was performed on the mean last post-baseline value of the HAM-D_{17} core subscale. For all the meta-analyses, Cochran homogeneity test was performed in addition to I^2 degree of inconsistency and forest plots.

Statistical analyses were performed on SAS® software, version 9.2 (Cary, North Carolina). The type I error was set at 5% (two-sided tests).