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ORIGINAL INVESTIGATION

Agomelatine in the treatment of seasonal affective disorder

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Abstract
Rationale The novel antidepressant agomelatine acts as a melatonergic (MT_1 and MT_2) receptor agonist and as a serotonin-2C receptor antagonist. Previous studies showed that agomelatine is able to restore disrupted circadian rhythms, which were implicated in the pathophysiology of seasonal affective disorder (SAD).
Objectives The aim of this study was to investigate the efficacy and tolerability of agomelatine in the treatment of SAD.
Materials and methods Thirty-seven acutely depressed SAD patients were included in an open study with agomelatine (25 mg/day in the evening) over 14 weeks. Efficacy assessments included the Structured Interview Guide for the Hamilton Depression Rating Scale (SAD version; SIGH-SAD), the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I), the Circscreen, a self-rating scale for the assessment of sleep and circadian rhythm disorders, and the Hypomania Scale.
Results Agomelatine led to a progressive and statistically significant decrease of SIGH-SAD, CGI-S, and CGI-I scores from week 2 onward ($p<0.001$). Furthermore, scores on the Circscreen improved significantly during the study ($p<0.001$). Treatment with agomelatine over 14 weeks yielded a response rate of 75.7% (SIGH-SAD <50% of baseline value) and a remission rate (SIGH-SAD <8) of 70.3% in the intention to treat sample. Scores on the Hypomania Scale were consistently low during the study. Agomelatine showed good overall tolerability: throughout the study only one adverse event (mild fatigue) was related to the study drug.
Conclusions The results of this study suggest that seasonal depression may be effectively and safely treated with agomelatine.

Keywords Depression · Seasonal affective disorder · SAD · Agomelatine · Antidepressant · Pharmacotherapy

Introduction

Seasonal affective disorder (SAD), according to the Diagnostic and Statistical Manual of Mental Disorder, (DSM-IV-TR) (American Psychiatric Association 2000), is a subtype of major depressive or bipolar disorder characterized by recurrent affective episodes at the same time of the year. Most frequently, patients suffer from depressive episodes during fall or winter (fall–winter depression), which are either followed by remission or hypomanic (rarely manic) episodes. Bright light therapy (BLT) was proposed as the treatment of choice for SAD (Winkler et al. 2006). However, a substantial proportion of patients with SAD requires antidepressant drug treatment either because of a lack of efficacy of BLT or because of logistic reasons or side effects (Pjrek et al. 2004).

Agomelatine[1] (S20098, *N*-[2-(7-methoxy-1-naphthyl) ethyl]acetamide) is a novel antidepressant agent with potent agonistic behavior at melatonergic (MT_1 and MT_2)-binding sites and antagonistic properties at the serotonin-2C receptor (Millan et al. 2003; Yous et al. 1992). The compound was shown to be effective in the treatment of major depressive disorder (Kennedy and Emsley 2006; Loo

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[1] Valdoxan®

et al. 2002). Furthermore, results from animal experiments (Grassi-Zucconi et al. 1996; Redman et al. 1995; Van Reeth et al. 2001) and studies in healthy humans (Leproult et al. 2005) suggest that agomelatine might have beneficial effects on disturbances of sleep and circadian rhythms.

This pilot study was aimed to evaluate the clinical usefulness of agomelatine in the treatment of SAD. A rationale for the use of a melatonergic antidepressant in SAD is provided by several studies implicating the indolamine hormone melatonin in the pathogenesis of the circadian rhythm disturbances found in depressed SAD subjects (Winkler et al. 2005). In mammals melatonin is produced by the pineal gland and mediates the length of the photoperiod by the duration of nocturnal secretion (Weaver 1999). SAD patients display a delay of dim light melatonin onset (Dahl et al. 1993; Sack et al. 1990) and a supersensitive melatonin suppression to light (Nathan et al. 1999). Some authors have also reported elevated serum concentrations of melatonin in SAD, especially during the daytime (Danilenko et al. 1994; Karadottir and Axelsson 2001; Levine et al. 1994), while others have failed to show abnormalities in melatonin production (Koorengevel et al. 2002).

Materials and methods

Thirty-seven outpatients (29 women and 8 men) with SAD were recruited at the outpatient clinic of the Department of General Psychiatry (Medical University of Vienna) between the first week of October and the second week of December for two consecutive years (2002–2003). Patients had to fulfill the criteria for a moderate or severe episode of recurrent major depressive disorder (296.32, 296.33) and the criteria for the seasonal pattern specifier according to the DSM-IV-TR. A global seasonality score of 11 or higher and a seasonal problem score of 2 (moderate) or higher on the Seasonal Pattern Assessment Questionnaire (Rosenthal et al. 1984) and a total score of 22 or higher on the Structured Interview Guide for the Hamilton Depression Rating Scale, SAD version (SIGH-SAD, 29 items; Williams et al. 2002) was required.

Patients with subsyndromal SAD (Kasper et al. 1989a), with a bipolar course of illness or with psychiatric comorbidity, were excluded from the study after screening with the Mini-international Neuropsychiatric Interview (Sheehan et al. 1998). Furthermore, patients with psychotic features, acutely suicidal patients, patients with a suicide attempt in the last 6 months, pregnant or breast-feeding females or women without adequate contraception, patients with severe physical illness interfering with the study, and those who had participated in a clinical trial in the last 3 months were excluded. The use of psychotropic medication and other drugs that were expected to interfere with the study was prohibited. A washout period before screening was specified for each of the disallowed medications, ranging from 1 week for most antidepressants (including herbal medication), zolpidem and zopiclone, systemic corticosteroids, ACTH, central alpha-adrenergic agonists, reserpine, methyldopa, exogenous melatonin, and opioides; 2 weeks for nonselective MAO inhibitors, benzodiazepines, and buspirone; 3 weeks for fluoxetine (if the duration of treatment had been longer than 7 days); 4 weeks for lithium, antiepileptics, barbiturates, and antipsychotics; to 6 months for long-acting depot neuroleptics. The initiation, modification, or discontinuation of beta-receptor blockers (during and 4 weeks before the study), thyroid hormones, or hormone replacement therapy (during and 3 months before the study) was also an exclusion criterion. Shift work, transatlantic flights, and travels in southern regions (longer than 2 weeks) in the first 10 weeks of the trial were disallowed by the protocol. Patients with therapeutic sleep deprivation during the last week, those treated with BLT during the last 4 weeks, and patients who had undergone electroconvulsive therapy or formal psychotherapy during the last 3 months were not eligible for this study.

Study subjects received treatment with open-label agomelatine as monotherapy for 14 weeks in a fixed dosage of 25 mg/day in the evening. Study visits after screening (visit 1, week −1) were scheduled as follows: visit 2 (baseline, first treatment), week 0; visit 3, week 2; visit 4, week 4; visit 5, week 6; visit 6, week 10; and visit 7 (endpoint), week 14. From visit 2 to 7 patients were rated with the SIGH-SAD, the Clinical Global Impression of Severity (CGI-S; Guy 1976), and the Hypomania Scale (Kasper et al. 1989b). The Clinical Global Impression of Improvement (CGI-I) was assessed at each visit from visit 3 onward. Patients completed the Circscreen (Laredo et al. 2002), a self-rating scale for the assessment of sleep and circadian rhythm disorders at visit 2, 5, and 7.

Primary outcome measures were SIGH-SAD total score and response and remission rates, which were computed from SIGH-SAD score; response was defined as a reduction of SIGH-SAD total score of more than 50% from baseline score. Remission was defined as a SIGH-SAD total score of less than 8 points. Secondary outcome measures included three SIGH-SAD subscales (the Hamilton 21-item scale, the atypical 8-item scale, and the Hamilton 6-item scale; Bech et al. 1981), CGI-S, CGI-I, and the Circscreen score (sum of items 1–5 measuring sleep disturbances and daytime fatigue; Table 1). Patients, who had not responded to agomelatine within the first 6 weeks of treatment, and those who had not achieved remission until week 10 were excluded by the protocol. This study was approved by the Ethics Committee of the Medical University of Vienna. All study procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki

Table 1 The first 5 items of the Circscreen (Laredo et al. 2002)

During the past 7 days:
1. Did you experience difficulties falling asleep at night?
2. Did you experience repeated awakening?
3. Did you wake very early in the morning, with difficulties falling asleep again?
4. Did you have difficulty becoming wide awake in the morning?
5. Did you feel sleepy during the daytime?

All these items of this questionnaire are rated by the patient on a 5-point scale: 0 very rarely, 1 rarely, 2 sometimes, 3 often, and 4 very often.

(World Medical Association General Assembly 2004). All subjects provided written informed consent before their inclusion in the study.

Statistical analyses were performed in the intention to treat sample with SPSS for Windows (SPSS 1989–2003) employing a last observation carried forward (LOCF) approach for missing data. We analyzed our data with univariate repeated measures analysis of variance (ANOVA) and Bonferroni corrected post hoc tests for comparisons between the study visits. Mauchly's test was calculated to check for violations of the sphericity assumption, and the Huynh–Feldt correction was applied whenever the assumption was not met. Furthermore, we made use of Kaplan–Meier survival analysis for estimation and graphical presentation of response and remission. Results were considered significant at $p \leq 0.05$. All statistical tests were two-tailed.

Results

The mean age of the patients in this sample was 38.8±13.0 years (mean±SD, range 20 to 60 years). Patients obtained a mean global seasonality score of 15.4±2.8 and a mean seasonal problem score of 3.4±0.8. Nineteen subjects (51.4%) fulfilled the DSM-IV-TR criteria for the atypical feature specifier and six (16.2%) for the melancholic feature specifier. The severity of depression was moderate in 27 cases (73.0%) and severe in 10 cases (27.0%).

SIGH-SAD total score at screening and baseline was 29.2±4.5 and 29.8±4.6, respectively. Hamilton 21-item score was 17.0±3.3 and 16.9±3.9, atypical 8-item score was 12.2±3.6 and 12.9±3.3, and Hamilton 6-item score was 9.1±1.5 and 9.1±1.8 at the screening and baseline visit, respectively. Analysis with repeated measures ANOVA yielded a significant effect of time on SIGH-SAD total score [$F(2.501)=104.948$, $p<0.001$; Fig. 1]. Post hoc tests confirmed a highly significant reduction of SIGH-SAD total score from week 2 onward ($p<0.001$). Treatment effects were progressive and sustained throughout the course of this trial: SIGH-SAD total score further

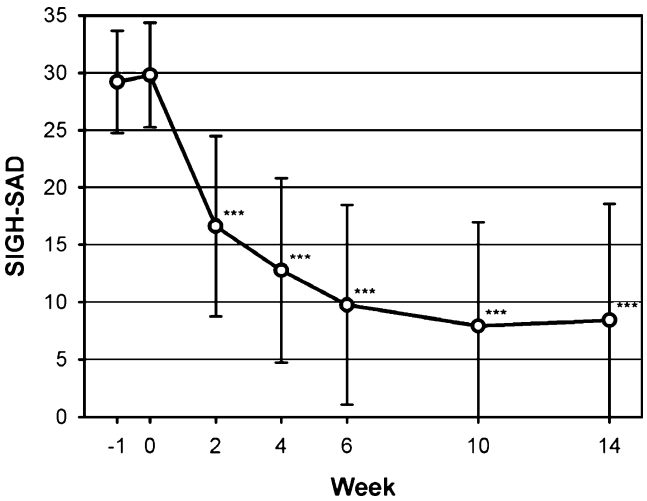

Fig. 1 Total score on the SIGH-SAD by week (mean±SD, LOCF, $N=37$). ***$p<0.001$

decreased to 8.4±10.1 until week 14 ($p<0.001$). Consecutively performed repeated measures ANOVAs resulted in a similar effect of time on the Hamilton 21-item scale [$F(2.885)=71.440$, $p<0.001$], the atypical 8-item scale [$F(2.733)=89.487$, $p<0.001$], and the Hamilton 6-item scale [$F(2.992)=73.051$, $p<0.001$] with statistical significance from week 2 onward ($p<0.001$ for all three measurements). Until week 14 there was a further decline of the Hamilton 21-item score, the atypical 8-item score, and the Hamilton 6-item score to 5.4±7.1, 3.0±3.8, and 2.9±3.6, respectively ($p<0.001$ for all three variables).

CGI-S score was 4.5±1.0 at baseline. CGI-S [$F(2.908)=52.803$, $p<0.001$] and CGI-I score [$F(3.167)=88.404$, $p<0.001$] both decreased significantly from week 2 onward ($p<0.001$ for both measurements). By week 14 the CGI-S score was as low as 1.9±1.3 ($p<0.001$) and the CGI-I score was diminished to 1.6±1.0 ($p<0.001$). The Circscreen score also improved during treatment with agomelatine [$F(2)=19.176$, $p<0.001$; Fig. 2] and showed a statistically significant reduction at week 6 ($p<0.001$) and week 10 ($p<0.001$).

After 14 weeks 75.7% of the patients had responded to treatment with agomelatine according to the above-defined criteria and 70.3% satisfied the criteria for remission (Fig. 3). The median time to response was 29 days [95% confidence interval (CI) 26–32 days], the median time to remission was 49 days (95% CI 40–58 days).

In total, there were ten adverse events during the 14 weeks of this study; nine of these adverse events were not related to the study drug. One patient reported daytime fatigue during the first 5 days of treatment, which was documented as an adverse event. Twelve more patients reported mild sleepiness after the intake of the medication in the evening during the first days of treatment, which was not associated with subjective impairment or tiredness

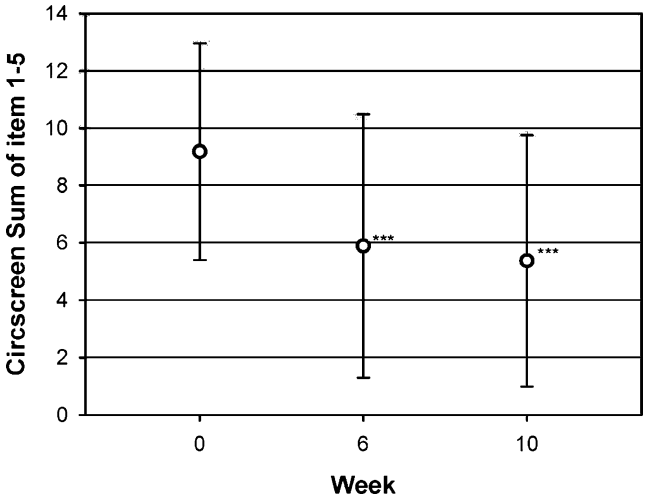

Fig. 2 Sum of items 1–5 of the Circscreen by week (mean±SD, LOCF, N=35). ***p<0.001

during the day. Scores on the Hypomania Scale were consistently low throughout the study (visit 2: 0.3±0.6, visit 3: 0.1±0.4, visit 4: 0.1±0.3, visit 5: 0.2±0.5, visit 6: 0.1±0.3, and visit 7: 0.2±0.4) and did not change significantly [F(3.399)=1.040, p=0.383]. Thirty subjects (81.1%) completed this trial. Three subjects (8.1%) dropped because of a lack of compliance, two of these patients dropped before baseline, i.e., before receiving any medication. Four subjects were withdrawn from the study because of a lack of efficacy (after 24, 34, 34, and 47 days of treatment). There were no dropouts due to side effects of the study drug.

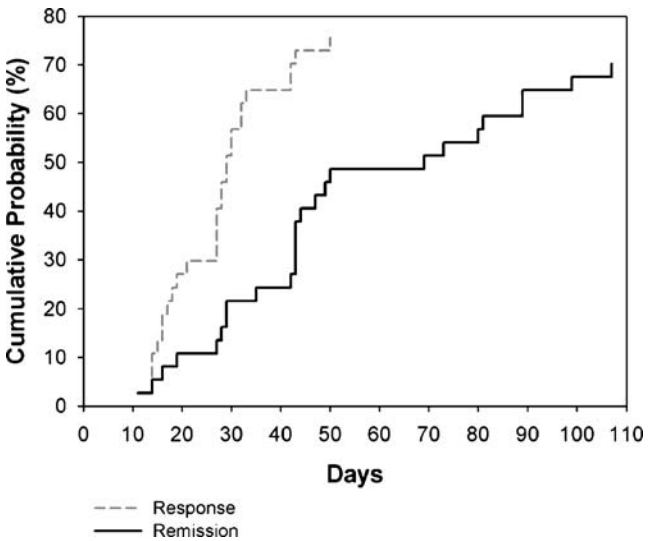

Fig. 3 Cumulative probability (%) of response (SIGH-SAD score <50% of baseline value) and remission (SIGH-SAD score <8) of 37 SAD patients during 14 weeks of treatment with agomelatine

Discussion

To our knowledge this is the first report on treatment effects of the melatonergic antidepressant agomelatine in SAD. Treatment with agomelatine had an onset of action after 2 weeks as evident by significant changes on most outcome variables. Moreover, a significant reduction of the patient rated Circscreen score after 6 and 10 weeks demonstrates that the use of agomelatine was associated with improvements of sleep disturbances and daytime fatigue. In contrast to trials investigating melatonin in SAD, which have not yielded a clear proof of efficacy (Leppamaki et al. 2003; Lewy et al. 1998, 2003), the antidepressant effectiveness of agomelatine is substantiated by a large percentage of patients experiencing sustained remission during the 14 weeks of this study.

Agomelatine displayed excellent tolerability at a daily dose of 25 mg and was virtually devoid of the side effects typical of other antidepressants, such as the selective serotonin reuptake inhibitors (Pjrek et al. 2006). About one third of our patients noticed mild sleepiness after the intake of the study drug during the first days of treatment. However, only one patient experienced subjective impairment due to daytime fatigue during the first 5 days after the initiation of treatment. It is interesting to note that the mild sedative potential of agomelatine did not cause major problems and did not lead to cessation of treatment in the subgroup of mostly hypersomniac SAD patients suffering from atypical depression. This is important as most SAD patients, especially those with a mild depressive syndrome, are not willing to tolerate a medication associated with unpleasant side effects.

The limitations of this study include the open design, the lack of a control group, and the relatively small sample size. Furthermore, our four subjects that were withdrawn from the study due to a lack of efficacy might have improved after a dose increase of agomelatine to 50 mg daily, which was not possible in this fixed-dose trial. This report adds to our current knowledge regarding the psychopharmacological treatment of SAD: Agomelatine is effective and in line with the demand for antidepressant drugs with a favorable side effect profile and improved safety. However, larger double blind, randomized, placebo-controlled trials and controlled studies with active comparators (including BLT) are needed to further define the clinical value of agomelatine as a treatment for SAD.

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