ABSTRACT

Objectives: The aim of this non-interventional, investigator driven study was to assess the functionality of patients with major depression under treatment with agomelatine in real life clinical practice.

Material and methods: The study was multicenter, non-interventional and evaluated the functionality of the adult patients with a DSM-IV diagnosis of MDD (single or recurrent episode and no treatment in the previous 6 months). It took place in Romania and it was a 10-weeks study. After the clinicians took the medical decision of treatment with agomelatine and if the patient agreed to be evaluated more accurate in this study, in order to assess functionality, patients completed at each visit the Sheehan Disability Scale (SDS). Patients were assessed also with QIDS-C (Quick Inventory of Depressive Symptomatology), a measure of depression symptoms severity and CGI scale severity (CGI-S), CGI scale improvement (CGI-I) and therapeutic index. Also, data about demographics and disease were collected during clinical interviews and from medical records.

Results: The functionality as assessed with SDS showed a significant functional impairment at baseline with scores >6 for each of the 3 inter-related domains of work/school, social and family life. At the end of the study, all functional aspects were improved although a mild impairment still persist requiring further treatment. A total of 1191 patients were analyzed (mean age: 47 years, 68% female). Mean QIDS-16 total score at baseline was 14.3 and decreased over the 10-week prospective period to 2.3. Most patients were treated with agomelatine.

Conclusion: This study outcome confirms the fast on set of functionality improvement of agomelatine and further treatment need for the total remission of clinical depressive symptomatology after 10 weeks of treatment.

Keywords: major depressive disorder, antidepressant treatment, functionality, agomelatine
INTRODUCTION

According to the World Health Organization (WHO), depression is estimated to affect 350 million people worldwide (1). The most recent European report of size and burden of mental disorders dated 2011 shows that 30.3 millions of people are affected by unipolar depression in Europe (2). The WHO predicts that by 2020 depression will represent the primary cause of disability globally, second only to ischemic heart disease (3). These data are in line with the European report from 2011, which shows that the most important contributor to burden of disease in Europe is depression, accounting for 7.2% of the overall disease burden in Europe (2).

It is known that depression causes substantial impairment in daily functioning. Data show that social functioning decreases in correlation with increasing depressive severity as 18% of patients with minor depression had major problems with daily interaction, compared to 52% of patients with 7-9 symptoms of major depressive episode. In general, it is considered that depression is increasing the risk of social disability 23-fold over the general population (4).

Older studies showed that very small degrees of residual interepisode impairment in certain areas might persist in patients between episodes, especially in patients with recurrent MDD reaching a certain threshold number and/or lengths of episodes over the lifetime course of the disease. Even in the case of subthreshold depressive symptoms, the disability is present (5). Consistent with these data, more recent studies highlight the relationship between the severity of depression and work function, suggesting that even minor levels of depression are associated with a loss of productivity (6). For the Romanian patients with major depressive disorder there were no data on functionality and we considered an opportunity to evaluate a new antidepressant effect on this aspect.

The aim of this study was to assess daily functionality in Romanian patients with major depressive disorder, single or recurrent episode, if they had previously been initiated the treatment with agomelatine. Additionally, the study explored the severity of depressive symptomatology of the study cohort, the study and the patients’ management, including treatment adherence.

MATERIALS AND METHODS

Study design and patient population

This 10-week multi-center prospective non-interventional study was conducted in 64 Romanian centers from the public system (outpatients or inpatients) or private practice in urban areas if they had been previously initiated by their clinician the treatment with agomelatine. After the psychiatrist took the medical decision the patients were asked if they want to be evaluated more accurate in this study.

The study population consisted of adult patient’s men and women diagnosed with major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (7) criteria and no previous treatment for single episodes or no treatment in the last 6 months for recurrent episodes. The exclusion criteria: age <18 years, presentation in emergency setting, use of psychoactive substances and conditions affecting patients’ participation to study such as limited cooperation, other serious condition or conditions limiting the life-expectancy (cancer), substance abuse or severe cardiovascular disease, kidney or liver failure.

The new treatment strategy prescribed was based only on the psychiatrists’ choice.

All patients whom agreed to be monitored more accurately in this study signed written, informed consent. The study was conducted in accordance with ethical principles derived from the Declaration of Helsinki and Declaration of Madrid of World Psychiatric Association (1995).

Assessments

Patients meeting inclusion criteria were enrolled in the study and followed up for 10 weeks as following: at baseline (V1), at 2 (V2), 6 (V3) and 10 weeks (V4).

Socio-demographic and clinical data, including the new pharmacological treatment prescribed and adherence to treatment, were collected from medical records and clinical interviews. At each visit, same psychometric scales have been used, as following: in order to evaluate the patients’ functionality impairment the Sheehan Disability Scale (SDS) has been
used, due to the fact that assesses the functional impairments in 3 inter-related domains: work/school, social and family life (0: no impairment, 1-3: mild impairment, 4-6: moderate impairment, 7-9: marked impairment, 10: extreme impairment). The other psychometric evaluations included the QIDS-C for the assessment of the severity of depressive symptoms, CGI-S, CGI-I and efficacy therapeutic index.

Statistical analyses

An initial sample size of 900 patients was calculated (taking into consideration the data from literature on agomelatine effect), but in study were enrolled 1191 patients.

Descriptive statistics and tests have been used to identify the significant differences of variables between all visits. T-test paired has been used for means, ANOVA method for comparing the means between more than 2 subgroups, Z-test for percentages, \( \chi^2 \)-test for frequency of distribution. All data were normal distributed. All significant differences (\( p=0.05 \)) have been analyzed at 95% level of confidence (95% CI).

Statistical analysis was performed using SPSS software, version 13.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Patients’ characteristics

A total of 1191 patients were included in the analysis. 68% of patients were females and the mean age of cohort was 47 years. 62% of the patients presented with single, new episode.

Clinical characteristics of the patients are included in Table 1. At baseline the mean QDIS-C Score was 14.3, with a mean CGI-S score of 4.6.

The previous antidepressants treatments used by patients with recurrent depressive disorder were the following: doxepin (46% from the 104 patients that administered TC), sertraline and escitalopram (31, respectively 28% from the 211 patients administering SSRI), mirtazapine (53% from 288 patients receiving NaSSa), venlafaxine (47% from 256 patients with previous SNRI treatment) and tianeptine (85% from 160 patients from group ‘Others’).

Functionality

At inclusion, all mean scores for the 3 inter-related domains of SDS scale were above 6, as following: 6.4 for work/school, 6.3 for social life, and 6.3 for family life/home responsibilities. The mean number of days lost in the previous week of inclusion was 3.1 with a mean number of unproductive days of 4.6.

At V2 (week 2), SDS scores started to improve and this improvement continued and was sustained until the end of study, with significant differences between the different evaluation time points. At V4 (week 10), a mild impairment persisted, with a mean score of 2 for work/school, similar with social and family life/home responsibilities, where the mean was 1.9 for each. In terms of days lost, the improvement was net, for V4 being recorded a mean of 0.1 days.

Treatment outcome

All patients received treatment during the study and almost all were treated with agomelatine (1188 patients at V1, respectively, 1175 patients at V4), for most the initial dosage of 25 mg being maintained for the entire period of study.

The mean QDIS-C score during the 10-week prospective follow-up decreased from 14.3 at baseline to 7.5 at V2, 4.3 at V3 and 2.3 at V4. The differences between all visits were considered statistically significant (\( p=0.05 \)). The symptoms whom more than 50% patients had scores of 2 at baseline were insomnia at beginning of sleep and insomnia early in the morning, mood and concentration/thinking.

The CGI-S score at V4 was significantly lower, decreasing from 4.6 to 1.8.

Improvement of disease, as assessed by CGI-I scale was observed already after 2 weeks of treatment (mean of 2.6) and continued to improve at V4 (mean of 1.4), a very small number of patients from one visit to another being rated with “no change” (5% of patients at V2, 1% at V3 and <1% at V4). The trend of net improvement during the study for all psychometric scales used is shown in Figure 1.

The efficacy index of the CGI-scale showed the improvement of disease based on treatment efficacy with a mean score of 2.1 at V2 (week 2) and 1.2 at V4 (week 10), the difference between visits being considered significant (\( p=0.05 \)).
There were no treatment emergent adverse events reported.

Treatment adherence was evaluated a very good (98.9%), a very low number of patients interrupting the treatment under study (n=26), mainly because of insufficient treatment.

**DISCUSSION**

Consistent with published data, this study confirms that in Romania more women than men are affected by depression (ratio of 2:1.2). More than 70% of patients from the study cohort were aged more than 40 years and more than half of the patients presented with a single episode of major depression.

The functional impairment at baseline was moderate to severe and after only 10 weeks of treatment was reduced to mild impairment.

The symptomatology had a moderate intensity at baseline as assessed with both QDIS-C and CGI-S. Even though more than half of the patients presented with new episodes, 36% of patients had recurrent episodes with residual symptoms impairing patients’ functionality so that they needed specialized care after at least 6 months of no treatment.

The study results emphasize the importance of the treatment as shown by the net improvement of all psychometric scales used in the study. Baseline data indicate that the more severe depression was, the greater the amount of productivity loss and disruption level of work/school, social and family life.

After 10 weeks of treatment, both symptomatology and functionality showed clear improvement and the trend of improvement was slower for functionality as the patients declared that the symptoms still disrupted their work/school work, social/life/leisure activities and family life/responsibilities in the last week. Despite the fact that no more days have been lost due to symptoms, after 10 weeks of treatment some patients still declared at least one day with loss of productivity. These results are in line with previous studies showing that depression has the potential to impact productivity (6).

Agomelatine was well tolerated and efficacious, improvements occurring as early as Week 2. These findings are in line with data from previous studies that demonstrated a rapid antidepressant efficacy (8). In the same time, this almost exclusive treatment with agomela-
tine represents a study limitation, as this does not allow comparisons with other treatment options.

Another study limitation is the relative small duration of the prospective period – 10 weeks, which doesn’t allow for observation of evolution and long-term adherence to treatment and further evolution of functionality.

CONCLUSION

Patients’ functionality was clearly improved over the 10-weeks treatment, but a mild impairment of daily functioning persisted in all domains analyzed: work/school, social and family life, which shows the need of continuous treatment management of depression. Moreover, 10 weeks of treatment were insufficient to restore complete remission.

In conclusion, the treatment with agomelatine provided an early improvement of symptomatology (week 2) and sustained over the 10-weeks period, but the treatments have to be continued as all international clinical guidelines recommend.

Conflict of interests: The corresponding author declares that he received grant from Servier Pharma for this study and other speaker fees. In addition, Dr. Valentin Matei and Dr. Victor Marinescu were in the past speakers for Servier Pharma and others companies.

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REFERENCES