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Efficacy of vortioxetine monotherapy compared with combined therapy vortioxetine and olanzapine in the treatment of major depression – first results

Účinnosť monoterapie vortioxetínom v porovnaní s kombinovanou liečbou vortioxetínom a olanzapínom v liečbe depresie – prvé výsledky

Original Paper

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Abstract Vortioxetine is a novel antidepressant with two mechanisms of action – direct effect on several serotonin receptors and serotonin reuptake inhibition. Atypical antipsychotics, such as olanzapine, used in the augmentation of antidepressants causes not only a better response to treatment, but also increased number of remissions. The aim of our work was to evaluate the efficacy of vortioxetine monotherapy compared to the combined treatment vortioxetine and olanzapine in adult patients with depression during the acute phase of treatment lasting 6 weeks. Depressive symptomatology was assessed by the MADRS scale, anxiety symptoms were assessed by the HAM-A scale and global clinical impression were evaluated by the CGI-S scale. The number of patients in full-analysis set was 28. The results showed statistically significant improvement in CGI-S for both groups. Patients with vortioxetine monotherapy showed significant improvement in MADRS total score from the third week of treatment ($p = 0.009$) compared to patients with combined therapy that showed significant improvement since the end of first week of treatment ($p = 0.036$). Both groups showed significant improvement in HAM-A total score from the second week of treatment. Our results show the possibility of olanzapine in the augmentation strategy in treatment of major depressive disorder in adult patients.

Slovak abstract Vortioxetín je nové multimodálne antidepresívum s dvomi mechanizmami účinku – priamym efektom na niektoré sérotonínové receptory a inhibíciou spätného vychytávania sérotonínu. Atypické antipsychotiká, ako je olanzapín, používané ako augmentácia antidepresívnej liečby, spôsobujú nielen lepšiu odpoveď na liečbu, ale aj vyšší počet remisií. Cieľom našej štúdie bolo zhodnotiť účinnosť monoterapie vortioxetínom v porovnaní s kombinovanou liečbou vortioxetín a olanzapín v rámci liečby akútnej fázy depresie počas 6 týždňov. Depresívnu symptomatiku sme hodnotili podľa škály MADRS, úzkostnú symptomatiku podľa škály HAM-A a celkový klinický dojem podľa škály CGI-S. Analyzovaný počet pacientov bol 28. Výsledky ukázali významné zlepšenie v škále CGI-S u oboch terapeutických vetiev. U pacientov liečených vortioxetínom v monoterapií došlo k významnému zlepšeniu v škále MADRS na konci tretieho týždňa liečby ($p = 0.009$), v porovnaní s pacientami liečenými kombinovanou liečbou, kde došlo k zlepšeniu v škále MADRS už na konci prvého týždňa liečby ($p = 0,036$). Obe skupiny preukázali významné zlepšenie v škále HAM-A počas druhého týždňa liečby. Naše výsledky poukazujú na možnosť použitia olanzapínu v rámci augmentačnej stratégie liečby depresívnej poruchy u dospelých pacientov.

Keywords *Vortioxetine – Olanzapine – Depression*

Kľúčové slová: *Vortioxetín – Olanzapín – Depresia*

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INTRODUCTION

Major depressive disorder (MDD) is a disease with lifetime prevalence of around 13% and incidence rate of 4%.[1] It presents a great burden to individuals with reduction of overall functioning.[2] Despite a large number of antidepressants, complete remission of depressive symptomatology is achieved only in 30 to 40% of patients with MDD treated with antidepressants from SSRI and SNRI group.[3] Also, the sexual dysfunction is a problem when using conventional antidepressants. From the findings of meta-analysis focused on the incidence of serious sexual dysfunction, only antidepressant without serotonergic activity were able to maintain low levels of sexual dysfunction similar to placebo.[4]
Vortioxetine is a novel antidepressant with multimodal mechanism of action: it acts on several serotonin receptors (5-HT1A agonist, 5-HT1B partial agonist and 5-HT1D, 5-HT3 and 5-HT7 antagonist), but it also causes serotonin reuptake inhibition through inhibition of serotonin transporter (SERT). In experimental studies, vortioxetine showed the normalization of serotoninergic, noradrenergic, and dopaminergic transmission. It is proved that vortioxetine is efficacious in various types of depression; in addition, it is also efficacious in patients who did not respond sufficiently to SSRIs and SNRIs treatment. Furthermore, vortioxetine is well tolerated with low rates of sexual dysfunction despite the patient's serotoninergic activity. Vortioxetine also showed statistically significant improvement in cognitive functions in depressed patients.[5]
Olanzapine is an atypical antipsychotic from the MARTA group (multi acting receptor targeted agents) structurally related to clozapine with no risk of agranulocytosis. It has an affinity for several serotonin (5-HT2A, 5-HT2C, 5-HT3 and 5-HT6), dopamine (D1-5), acetylcholine (M1-5), α1-adrenergic and histamine H1 receptors.[6] Olanzapine agonism at 5-HT1A receptors result in an increased release of noradrenaline in the prefrontal cortex and ncl. accumbens, which is associated with improvement in cognitive function. Its antagonism on the 5-HT2A receptors enhances the release of noradrenaline and serotonin, resulting in a reduction of suppression of firing in the locus coeruleus induced by SSRIs. Moreover, the increased release of dopamine in the prefrontal cortex leads to an improved regulation of mood and cognitive function.[7]
The aim of our work was to evaluate the efficacy of vortioxetine monotherapy compared to a combined treatment of vortioxetine and olanzapine in adult patients with MDD.

MATERIAL AND METHODS

The design of the study was open-label clinical randomized trial without blind testing or using placebo control group. The duration of the study was 6-weeks.

The including criteria were diagnosis of depressive episode (F32) or recurrent depressive disorder (F33) according to ICD-10 classification, age 18–65 years and the ability to participate in the study. The excluding criteria were serious symptomatic disease, which could distort the results and cognitive deficit that did not allow adequate cooperation in the study. Eligible patients were randomized (1:1) into two equal therapeutic groups (vortioxetine monotherapy, vortioxetine and olanzapine combined therapy). Vortioxetine was dosed from 10 to 20 mg per day, olanzapine was dosed from 5 to 10 mg a day.
The depressive and anxious symptomatology was evaluated by standard scales used in psychiatric research every week during the acute phase of treatment lasting 6 weeks. Depressive symptomatology was assessed by the 10-item MADRS scale (Montgomery and Asberg Depression Rating Scale). The anxiety symptoms were assessed by the 15-item HAM-A scale (Hamilton Anxiety Rating Scale). Also, the global clinical impressions were evaluated by the CGI-S scale (Clinical Global Impression - Severity). After that, the mean MADRS, HAM-A and CGI-S total scores were calculated and statistically assessed by using non-parametric t-test and ANOVA for comparison of efficacy of treatment in each therapeutic group and Kruskal-Wallis test for inter-group comparison.

RESULTS

From the 29 patients included in the study, 28 went for the full-analysis set (FAS), 14 in each therapeutic group, with one drop-out from the study.
The results of t-test from the CGI-S scale showed statistically significant improvement in both groups. The mean CGI-S score in patients on vortioxetine monotherapy was 5.1 ± 0.7 in the first week compared to 2.7±0.9 in the sixth week of treatment. The CGI-S mean score in patients on combined therapy was 5.4±0.8 in the first week compared to 2.4±1.5 in the sixth week of treatment. There were no significant differences between groups.

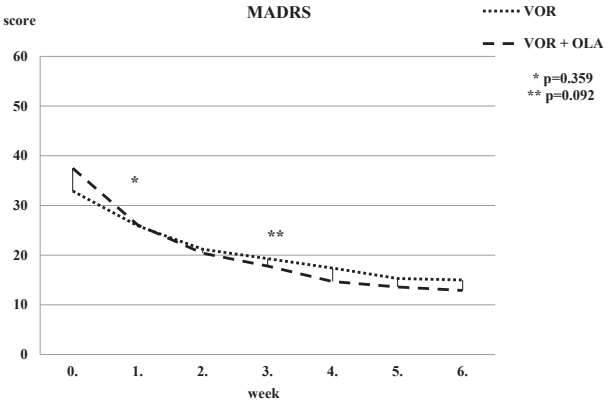

Figure 1. MADRS total score dynamics during the treatment. VOR – vortioxetine, OLA – olanzapine

Both groups showed a statistically significant decrease in MADRS total score after 6 weeks of treatment. Patients treated with vortioxetine monotherapy had mean MADRS total score 32.9±7.1 in the first week and 15±7.5 after six weeks of treatment with p = 0.0004. Patients treated with combined therapy had mean MADRS total score 37.5±6.6 in the first week and 12.9±12.9 after six weeks of treatment with p = 0.0031. The dynamics of decreasing MADRS total score during the treatment is shown in Figure 1. Patients with vortioxetine monotherapy showed significant improvement from the third week of treatment (p = 0.009) compared to the patients with a combined therapy that showed significant improvement since the end of first week of treatment (p = 0.036). There was no statistical significance between the groups in MADRS total score.

Both groups showed a statistically significant decrease in HAM-A total score after 6 weeks of treatment. Patients with vortioxetine monotherapy had mean HAM-A total score 27.9±4.3 in the first week and 13.5±5.8 after six weeks with p = 0.0001. Patients treated with combined therapy had mean HAM-A total score 30.3±10.1 in the first week and 10.9±10.1 after six weeks with p = 0.0052. Each group showed significant improvement from the second week of treatment with no significant difference between the groups. The dynamics of decreasing HAM-A total score is shown in Figure 2.

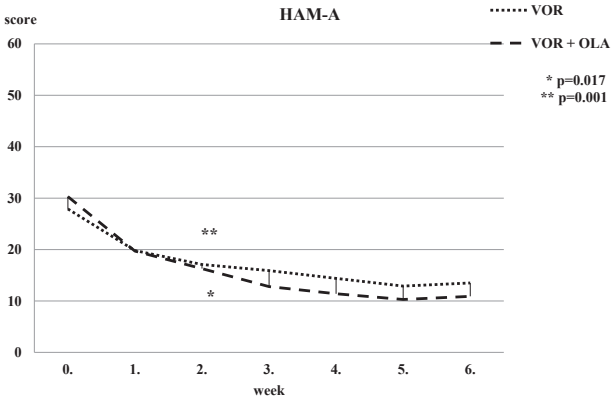

Figure 2. HAM-A total score dynamics during the treatment. VOR – vortioxetine, OLA – olanzapine

DISCUSSION

This study evaluated the efficacy of vortioxetine monotherapy compared to the combined therapy vortioxetine and olanzapine after 6 weeks of treatment in adult patients with depression. Clinical relevance was shown by an improvement in the CGI-S score in both groups.

Vortioxetine efficacy in reducing the depressive symptoms has been proved in 8 out of 12 short-term (6, 8 or 12 weeks) clinical trials[1] and it is consistent with the results of our study. The significant improvement in the MADRS total score was observed from the third week of treatment. However, the combined therapy with olanzapine showed significant improvement in the MADRS total score since the end of first week. These findings suggest the augmentation effect of olanzapine on reducing depressive symptomatology. The results from studies showed that typical antipsychotics are not sufficiently effective in reducing at least two symptoms of depression, which are loss of interest and psychomotor inhibition,[8] but atypical antipsychotics used in augmentation of antidepressants causes not only a better response to treatment, but also an increased number of remissions.[9]

In both groups, we showed significant effect in reducing anxiety symptoms demonstrated by a decrease of HAM-A total score from the second week of treatment. It could be beneficial in the treatment of depression, because in approximately half of all individuals with MDD, high levels of anxiety symptoms are observed.[10] The anxiolytic efficacy of vortioxetine is also proved in the treatment of generalized anxiety disorder based on the results of recent meta-analysis of data from 4 short-term, randomized controlled trials.[11]

Our results show the possibility of olanzapine in the augmentation strategy in treatment of major depressive disorder in adult patients with an effect in reducing depressive symptomatology.

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