Abstract

Introduction. Deutetrabenazine is FDA-approved for the treatment of tardive dyskinesia (TD) in adults. In two 12-week pivotal trials (ARM-TD/AIM-TD), deutetrabenazine significantly improved Abnormal Involuntary Movement Scale (AIMS) scores and was well-tolerated. This post hoc analysis examined the efficacy and safety of long-term deutetrabenazine treatment in TD patients with comorbid psychiatric illness, including schizophrenia/schizoaffective disorder and mood disorders (bipolar/depression/other).

Methods. Patients who completed ARM-TD or AIM-TD enrolled in the 3-year, open-label extension (OLE) study. Deutetrabenazine was titrated based on dyskinesia control and tolerability. Change from baseline in total motor AIMS score, Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and adverse events (AEs) were analyzed in subgroups by comorbid psychiatric illness.

Results. A total of 337 patients in the OLE study were included in the analysis: 205 patients with schizophrenia/schizoaffective disorder (mean age, 55 years; 50% male; 6.4 years since diagnosis; 92% taking DRA) and 131 patients with mood disorders (mean age, 60 years; 35% male; 4.6 years since diagnosis; 50% taking DRA). At week 145, mean ± SE dose was 40.4 ± 1.1 mg/day for schizophrenia/schizoaffective disorder (n = 88) and 38.5 ± 1.2 mg/day for mood disorders (n = 72). Mean ± SE change from baseline in AIMS score at week 145 was −6.3 ± 0.49 and −7.1 ± 0.58, 56% and 72% achieved PGIC treatment success, and 66% and 82% achieved CGIC treatment success in schizophrenia/schizoaffective disorder and mood disorder patients, respectively. Overall AE incidence (exposure-adjusted incidence rates [incidence/patient-years]) was low: any, 1.02 and 1.71; serious, 0.10 and 0.12; leading to discontinuation, 0.07 and 0.05).

Conclusion. Long-term deutetrabenazine treatment provided clinically meaningful improvements in TD-related movements, with a favorable safety profile, regardless of underlying comorbid psychiatric illness.

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Long-Term Efficacy and Safety of Deutetrabenazine in Patients with Tardive Dyskinesia by Concomitant Dopamine-Receptor Antagonist Use

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Abstract

Introduction. Tardive dyskinesia (TD) is an involuntary movement disorder that can result from exposure to dopamine-receptor antagonists (DRAs). Deutetrabenazine demonstrated significant improvements in Abnormal Involuntary Movement Scale (AIMS) scores in the 12-week pivotal trials (ARM-TD/AIM-TD). This post hoc analysis assessed the long-term efficacy and safety of deutetrabenazine by baseline DRA use.

Methods. Patients who completed ARM-TD or AIM-TD enrolled in the 3-year, open-label extension (OLE) study, with deutetrabenazine dose titrated based on dyskinesia control and tolerability. Change from baseline in total motor AIMS score, Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and adverse event (AE) rates were analyzed in subgroups by baseline DRA use.

Results. Of 337 patients in the OLE study, 254 were taking DRAs at baseline (mean age, 56 years; 48% male; 6.0 years since diagnosis) and 83 were not (mean age, 60 years; 31% male; 4.9 years since diagnosis). Mean ± SE dose at week 145 was 39.9 ± 1.0 mg/day in patients taking DRAs (n = 108) and 38.5 ± 1.5 mg/day in patients not taking DRAs (n = 53). At week 145, mean ± SE change from baseline in AIMS score was −6.1 ± 0.43 and −7.5 ± 0.71; 64% and 62% achieved PGIC treatment success; and 69% and 81% achieved CGIC treatment success, respectively. Overall AE incidence was low (exposure-adjusted incidence rates [incidence/patient-years]: any, 1.08 and 1.97; serious, 0.10 and 0.12; leading to discontinuation, 0.06 and 0.05).

Conclusion. This analysis suggests that deutetrabenazine for long-term treatment of TD is beneficial, with a favorable safety profile, regardless of concomitant DRA use.

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Effect of REL-1017 (Esmethadone) on Cholesterol, Triglycerides, PCSK9, and hs-CRP in a Phase 2a Double-Blind Randomized Trial in Patients with MDD

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Abstract

Background. Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality. Hyperlipidemia and vascular subinflammation play critical roles in the pathogenesis of atherosclerosis. Patients with Major Depressive Disorder (MDD) are at higher risk for ASCVD and current antidepressant therapies may carry ASCVD risks. REL-1017 is a novel NMDAR channel blocker which showed rapid, robust, and sustained antidepressant effects, currently in Phase 3 clinical trials for MDD.

Methods. We analyzed total cholesterol (TC), triglycerides (TG), Proprotein Convertase Subtilisin/Kexin 9 (PCSK9), and high-sensitivity C-reactive protein (hs-CRP) from patients enrolled in a Phase-2, multicenter, randomized, double-blind, placebo-controlled, 7-day, 3-arm trial to assess safety, tolerability, pharmacokinetics, and efficacy of REL-1017. Patients were randomized in a 1:1:1 ratio to either placebo, REL-1017 25 mg QD, or REL-1017 50 mg QD. TC, TG, PCSK9, and hs-CRP levels were measured in patients at baseline, day 7 and day 14, 7 days after treatment discontinuation. 6 out of 21 (28% of patients), 6 out of 16 (37%), and 1 out of 19 (5%), were under statin therapy in the placebo, REL-1017 25 and 50 mg groups, respectively.

Results. At baseline, day 7, day 14 TC levels (mg/dL) were 117.8 ± 30.8, 124.7 ± 34.1, 114.2 ± 18.1; 123.7 ± 59.3, 119.0 ± 28.1, 115.1 ± 14.8; 113.9 ± 22.9, 118.6 ± 29.5, 115.8 ± 25.5 for placebo (n = 21), REL-1017 25 mg (n = 16) and REL-1017 50 mg (n = 19), respectively. Considering the subgroup not on statins, TC levels were 127.5 ± 28.6, 134.2 ± 35.0, 117.8 ± 14.8; 131.0 ± 71.7, 121.1 ± 32.9, 118.6 ± 15.4; 115.5 ± 22.1, 121.4 ± 27.1, 119.0 ± 21.9 for placebo (n = 15, 72% of patients), REL-1017 25 mg (n = 10, 63%) and REL-1017 50 mg (n = 18, 95%), respectively. TG were 57.0 ± 25.6, 55.7 ± 20.0, 58.0 ± 34.1; 62.7 ± 52.1, 56.0 ± 31.0, 59.5 ± 32.6; 48.5 ± 25.3, 50.2 ± 18.4, 55.1 ± 21.9 for placebo (n = 21), REL-1017 25 mg (n = 16) and REL-1017 50 mg (n = 19), respectively. Considering the group not on statins, TG were 52.9 ± 27.6, 55.7 ± 23.1, 51.3 ± 26.8; 70.6 ± 63.3, 57.6 ± 38.9, 65.2 ± 38.9; 47.4 ± 25.4, 48.9 ± 17.9, 52.6 ± 19.5 for placebo (n = 15), REL-1017 25 mg (n = 10), and REL-1017 50 mg (n = 18), respectively. Levels of PCSK9, a key player of LDL cholesterol levels, significantly ($P < .05$) increased from baseline to day 7 and did not further change by day 14 for placebo, with similar results for REL-1017 25 or 50 mg groups, suggesting fluctuations unrelated to treatment. A total of 30% of the patients had hs-CRP plasma levels higher than 2 mg/L, thus potentially associated with a higher incidence of CV events. However, 7 days of treatment with REL-1017 did not alter hs-CRP plasma levels, neither at 25 mg/day nor at 50 mg/day. In summary, REL-1017 of 25 or 50 mg for 7 days did not affect TC, TG, PCSK9 and hs-CRP levels.

Conclusion. A 7-day treatment course with REL-1017 did not significantly alter TC, TG, PCSK9, or hs-CRP, suggesting the absence of detrimental effects on ASCVD risk. These data should be confirmed in longer and larger trials.

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