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Cryptococcal Meningitis Leading to Fatal Outcomes in Immunocompetent Patients: A Case Study and Review of Literature

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ABSTRACT: Introduction: Cryptococcal Meningitis is a fungal infectious disease of worldwide distribution, primarily associated with underlying immunosuppression conditions such as HIV infection, glucocorticoid treatment, status post organ transplantation and oncological treatments. Prevalence is particularly high in third-world countries where it constitutes one of the primary causes of central nervous system infections and may carry fatal outcomes. We present two cases of Cryptococcal Meningitis that portray the vast spectrum of clinical presentations associated with Cryptococcal Meningitis as well as relevant diagnostic and therapeutic implications.

METHODS: Case study - These adult otherwise healthy patients presented at a public urban university hospital in southern Colombia. Both had an unusual clinical course and suffered fatal outcomes despite being seemingly immunocompetent at baseline. A diagnosis of hepatic cirrhosis could have been considered a cause of immunosuppression in one of the patients and the diagnostic work-up for the other patient revealed no evidence of immunological deficiency.

DISCUSSION: Cryptococcal Meningitis affecting immunocompetent individuals has been increasingly reported in recent years. Furthermore, outcomes in this population are particularly worse than those generally affected by the disease. A review of the literature related to the possible immunological mechanisms' underlying the presented clinical course is included. We emphasize the importance of considering Cryptococcus spp. as a possible etiologic agent among differential diagnoses upon encountering suggestive meningeal conditions in immunocompetent patients.

Key words: Cryptococcus neoformans, Meningitis, Immunocompetent
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Lumateperone (ITI-007) for the Treatment of Schizophrenia: Overview of Placebo-Controlled Clinical Trials and an Open-label Safety Switching Study

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ABSTRACT: Background: Lumateperone is a first-in-class agent in development for schizophrenia that acts synergistically through serotonergic, dopaminergic and glutamatergic systems. Lumateperone is a potent 5-HT2A antagonist, a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with presynaptic partial agonist and post-synaptic antagonist activity at D2, a glutamate GluN2B receptor phosphoprotein modulator with D1-dependent enhancement of both NMDA and AMPA currents via the mTOR protein pathway and an inhibitor of serotonin reuptake.

METHODS: Lumateperone was evaluated in 3 controlled clinical trials to evaluate efficacy in patients with acute schizophrenia. The primary endpoint was change from baseline on the PANSS total score compared to placebo. In Study '005, 335 patients were randomized to receive ITI-007 60 mg or 120 mg , risperidone 4 mg (active control) or placebo QAM for 4 weeks. In Study '301, 450 patients were randomized to receive ITI-007 60 mg or 40 mg , or placebo QAM for 4 weeks. In Study '302, 696 patients were randomized to receive ITI-007 60 mg or 20 mg , risperidone 4 mg (active control) or placebo QAM for 6 weeks. Also, an open-label safety switching study was conducted in which 302 patients with stable schizophrenia were switched from standard-of-care (SOC) antipsychotics and treated for 6 weeks with lumateperone QPM and then switched back to SOC.

RESULTS: In Studies '005 and '301, lumateperone (60 mg ITI-007) met the primary endpoint with statistically significant superior efficacy over placebo at Day 28. In Study '302, neither dose of lumateperone separated from placebo on the primary endpoint; a high placebo response was observed in this study. Across all 3 efficacy

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trials, lumateperone improved symptoms of schizophrenia with the same trajectory and same magnitude of improvement from baseline to endpoint on the PANSS total score.
Lumateperone was well-tolerated with a favorable safety profile in all studies. In the two studies with risperidone included as an active control, lumateperone was statistically significantly better than risperidone on key safety and tolerability measures. In the open-label safety switching study statistically significant improvements from SOC were observed in body weight, cardiometabolic and endocrine parameters worsened again when switched back to SOC medication. In this study, symptoms of schizophrenia generally remained stable or improved. Greater improvements were observed in subgroups of patients with elevated symptomatology (comorbid symptoms of depression and those with prominent negative symptoms).

DISCUSSION: Lumateperone represents a novel approach to the treatment of schizophrenia with a favorable safety profile in clinical trials. The lack of cardiometabolic and motor safety issues presents a safety profile differentiated from standard-of-care antipsychotic therapy.
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A Modified-Release Drug Delivery Technology Containing Amphetamine-Ion Exchange Complexes

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ABSTRACT: The proprietary, immediate and extended drug delivery technologyLiquiXR® utilizes an ion-exchange resin that complexes with amphetamine or any active moiety that can be protonated and is water-soluble. The active ingredient of the drug product forms a complex with an ion exchange polymer of the resin resulting in micron-sized particles. A portion of these particles is then coated with an aqueous, pH-independent polymer designed to provide sustained release of drug product. The polymer coating applied to the ion-exchange resin particles is of varying thickness, allowing for extended release of active drug while uncoated particles provide for immediate release of drug.
The micron-sized particles lend themselves to being formulated into an appropriate dosage form: solid/chewable tablet, liquid suspension, orally disintegrating tablet, film, or capsules. Active ingredient of drug product is subsequently released from the dosage form in millions of particles, with release driven by a combination of ion exchange and diffusion. After drug release, the ion-exchange resin particles are excreted in the feces.
The release characteristics of LiquiXR allow for customized, sustained release of active drug ~24 hours post dose. Mechanistically, drug particles enter the gastrointestinal (GI) tract. As positively-charged ions from GI fluids diffuse across the coating, it displaces drug ions from product and they diffuse through the coating and into the GI fluids for absorption. As the coating is of variable thickness, some drug product takes longer to diffuse and absorb, providing for the delayed drug release characteristics.
The LiquiXR drug delivery technology has already been successfully utilized in the development of treatment options (liquid suspension and chewable tablet) that offer rapid absorption and sustained plasma levels after once-daily dosing. LiquiXR is utilized in Dyanavel® XR (amphetamine extended-release oral suspension; AMPH EROS), which is indicated for treatment of ADHD. It comprises 2.5 mg/mL amphetamine base and uses LiquiXR technology to provide an immediate release component followed by an extended-release profile.
Efficacy of AMPH EROS was established in children 6 to 12 yr in a Phase 3, placebo-controlled laboratory classroom study. In that study, ADHD symptoms in children on an individually optimized dose of amphetamine (range 10–20 mg/day) were statistically significantly improved compared with symptoms in children treated with placebo. For children treated with AMPH EROS, onset of effect was demonstrated at 1 hour after dosing, and efficacy was observed through 13 hr post-dose. The effect size (ES) was comparable to ES demonstrated for other psychostimulants tested in studies using a similar design. The efficacy data reported for AMPH EROS provides an excellent example of the potential utility and clinical application for other active drug products requiring an immediate and extended release profile.
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Early-Onset Efficacy and Safety Pilot Study of Amphetamine Extended-Release Oral Suspension (AMPH EROS) in the Treatment of Children with Attention-Deficit/Hyperactivity Disorder

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