Ultra-High-Dose Long-Acting Injectable Aripiprazole in Chronic Refractory Schizophrenia: A Case Report

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Abstract

An intramuscular long-acting injectable (LAI) aripiprazole administered once a month as a single injection into the gluteal muscle is increasingly appreciated in the course of a long-term maintenance treatment of schizophrenia. Due to efficacy in delaying and decreasing relapse, low rates of feared side effects including extrapyramidal, metabolic and cardiovascular disturbances, aripiprazole LAI has the potential to significantly improve adherence. According to the prescribing information, the maximal starting as well as maintenance dose of aripiprazole LAI is restricted to 400 mg following a 26-day interval between the single doses.

We present a case of a 72-year-old female inpatient with an acute exacerbation of chronic refractory schizophrenia treated with aripiprazole LAI (ABILIFY MAINTENA) beyond the officially approved dose range (up to 1200 mg per month). Applying this ultra-high-dose antipsychotic maintenance treatment over 12 weeks, we observed a clinically meaningful reduction of the initially severe psychopathological phenomena with primarily positive symptoms (a total-score reduction from 111 to 75 on the Positive and Negative Syndrome Scale; PANSS). Despite multi-morbidity and rather advanced age of the patient, no objectifiable adverse events, which were measured by The Dosage Record Treatment Emergent Symptom Scale (DOTES) and The Barnes Akathisia Rating Scale (BARS), occurred during the treatment.

Our safe experience with an almost threefold higher monthly dose might encourage researchers to further investigate the efficacy, tolerability as well as handling of highly dosed aripiprazole LAI as a maintenance treatment option in refractory schizophrenia.

Keywords: Refractory schizophrenia; Long-Acting injectable; Aripiprazole; High-dose treatment; Tolerability; Adherence

Introduction

Long-acting injectable (LAI) antipsychotics are increasingly appreciated in the course of maintenance treatment of schizophrenia playing an important role in improving adherence and preventing hospitalizations [1]. During the last decades, a growing number of second-generation antipsychotics (SGAs) became available as LAIs. Aripiprazole is a SGA acting via partial agonism on dopaminergic D2- and serotonergic 5-HT1A-receptors, as well as via full antagonism on 5-HT2A-receptors [2]. Since 2002, an intramuscular LAI formulation of aripiprazole is available and officially approved for the maintenance treatment of schizophrenia in patients with established tolerability to oral aripiprazole. Previous trials conducted in adult schizophrenia patients could show that aripiprazole LAI 400 mg administered once a month as a single injection into the gluteal muscle delays- and reduces relapse, is related to low rates of extrapyramidal, metabolic or cardiovascular side effects, and hence, has the potential to significantly improve adherence [3-5].

According to the prescribing information, oral aripiprazole (10 to 20 mg p.o.q.d.) should be administered prior to initiating aripiprazole LAI in order to establish tolerability, as well as on 14 consecutive days in conjunction with the first intramuscular injection in order to maintain therapeutic antipsychotic concentrations. Despite recent evidence demonstrating aripiprazole lauroxil, a novel LAI that is now in development for a high-dose treatment of schizophrenia [6], the maximum recommended starting as well as maintenance dose of the currently available aripiprazole LAI has been restricted to 400 mg following a 26-day interval between the single doses for a broad use in clinical routine [7].

Case Report

We report on a 72-years-old female inpatient (66 kg) suffering from chronic refractory schizophrenia according to the current versions of The International Statistical Classification of Disease and Related Health Problems (ICD-10) [8] and The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [9]. In spite of numerous antipsychotic treatment attempts including oral- as well as intramuscular administration of both first- and second-generation antipsychotics, co-medication with benzodiazepines and mood stabilizers, accompanied by thorough psychotherapeutic and psychosocial support, she remained refractory, exhibiting primarily positive symptoms such as excessive persecutory delusions. Consequently, she required frequent hospitalizations, mostly because of acute self-endangerment with extensive self-care deficit in the context of relapse or non-adherence. Eventually, olanzapine LAI 405 mg administered once a month at the outpatient unit of the Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria kept her psychopathology at a stable level without a
need for an inpatient care for approximately 18 months. However, this intramuscular long-term maintenance treatment was discontinued because of a serious adverse event, whereby the patient went comatose after an accidental intravascular administration (the so-called post-injection syndrome [10]), exhibiting olanzapine plasma concentration of 797.5 ng/ml (therapeutic range: 5-100 ng/ml). During her following stay at a psychiatric intensive care unit (PICU), she spent three days in coma, exhibiting pronounced hypotonia and tachycardia initially (09/2014). Once her vital parameters became stable again, and olanzapine plasma concentration declined to 24.8 ng/ml, the temporarily interrupted antipsychotic treatment was continued with oral olanzapine 20 mg p.o.q.d. (10/2014), which however, did not lead to comparable therapeutic effects. The reappeared severe psychotic symptoms including excessive persecutory delusions, suspiciousness, conceptual disorganization, disoriented and hallucinatory behavior, concrete and stereotyped thinking, as well as poor insight and insufficient adherence to continuous intake of oral medication made reinstating intramuscular treatment necessary. In detail, she refused food intake, threw away her keys, wandered around the city and slept at various places including night shelters for the homeless. After she was re-admitted to the PICU, the antipsychotic treatment was switched to aripiprazole 15 mg p.o.q.d. (11/2014). Once tolerability was established, aripiprazole LAI 300 mg was delivered into her gluteal muscle, while oral aripiprazole was co-administered on 14 consecutive days in conjunction with the first intramuscular injection (12/2014). After an initial stabilization and subsequent relocation from the PICU to a general psychiatry inpatient unit, she became acutely and severely psychotic again, whereby she ran away from the psychiatric ward, wandered around the city, and was finally returned by the police. At that time, she exhibited a total-score of 111 on the Positive and Negative Syndrome Scale (PANSS) [11]. Since reinstating oral aripiprazole and a dose increase of aripiprazole LAI to 400 mg per month (01/2015) did not lead to sufficient clinical improvement, aripiprazole LAI 400 mg was administered every 14 days under continuous plasma level monitoring (02/2015). As no relevant reduction of psychopathological symptoms was achieved, no objectifiable side effects assessed by “The Dosage Record Treatment Emergent Symptom Scale (DOTES)” [12] and “The Barnes Akathisia Rating Scale (BARS)” [13] occurred, and aripiprazole plasma concentration (162.9 ng/ml; therapeutic range: 150-500 ng/ml) allowed further dose-escalation, aripiprazole LAI was gradually increased up to 600 mg and administered every 14 days (03/2015). Here, 2 single injections of aripiprazole LAI 300 mg were delivered into both gluteal muscles concurrently. Consequently, we observed a significant reduction of psychotic symptoms (PANSS total-score: 75), which was not accompanied by relevant extrapyramidal, metabolic or cardiovascular side effects, as well as more common adverse events such as akathisia, insomnia or headache. Subsequently, oral aripiprazole was discontinued cautiously. Despite the almost threefold higher monthly dose of aripiprazole LAI resulting in an aripiprazole plasma concentration far beyond the therapeutic range (>668 ng/ml=non-measurable values), the patient did not develop any objectifiable adverse effects (04/2015).

In order to optimize the long-term maintenance treatment manageable also on outpatient basis, the administration of aripiprazole LAI was adapted to 800 mg (2 single injections of aripiprazole LAI 400 mg into both gluteal muscles) every 3 weeks (06/2015). Following this treatment regimen, the patient remained stable even after discharge from psychiatric inpatient care (PANSS total-score: 70-75).

Discussion

To our knowledge, this is the first report on an ultra-high-dose aripiprazole LAI (ABILIFY MAINTENA up to 1200 mg once monthly) as off-label intramuscular maintenance treatment in chronic refractory schizophrenia. The medication did not lead to extrapyramidal, metabolic or cardiovascular side effects as well as other adverse events, in a 72-years old patient with a number of comorbidities (arterial hypertension, mitral valve insufficiency, post-thrombotic syndrome).

Since we observed a clinically meaningful reduction of the initially severe psychotic symptoms (PANSS total-score reduction from 111 to 75), our safe experience with almost threefold higher monthly dose might encourage researchers to further investigate the efficacy and tolerability of a high dose aripiprazole LAI as a maintenance treatment option for refractory schizophrenia. Furthermore, since two single intramuscular injections are necessary to apply 600 mg or 800 mg of aripiprazole LAI, which is challenging when administered once or twice monthly, a handing-improvement would be highly appreciated.

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