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Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia ☆

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ABSTRACT

Background: Cognitive dysfunction is a key predictor of functional disability in schizophrenia. Davunetide (AL-108, NAP) is an intranasally administered peptide currently being developed for treatment of Alzheimer's disease and related disorders. This study investigates effects of davunetide on cognition in schizophrenia.
Method: Sixty-three subjects with schizophrenia received davunetide at one of two different doses (5, 30 mg) or placebo for 12 weeks in a multicenter, double-blind, parallel-group randomized clinical trial. The MATRICS Consensus Cognitive Battery (MCCB) assessed cognitive effects. The UCSD Performance-based Skills Assessment (UPSA) and the Schizophrenia Cognition Rating Scale (SCoRS) assessed functional capacity. Subjects continued their current antipsychotic treatment during the trial.
Results: There were no significant differences in MCCB change between davunetide and placebo over the three treatment arms ($p = .45$). Estimated effect-size (d) values were .34 and .21 favoring the 5 and 30 mg doses vs. placebo, respectively. For UPSA, there was a significant main effect of treatment across study arms ($p = .048$). Between-group effect size (d) values were.74 and .48, favoring the 5 and 30 mg doses, respectively. No significant effects were observed on the SCoRS or on symptom ratings. No significant side effects or adverse events were observed.
Conclusion: Davunetide was well tolerated. Effects of davunetide on MCCB-rated cognition were not significant relative to placebo. In contrast, a significant beneficial effect was detected for the UPSA. Based upon effect-size considerations, sample sizes of at least 45–50 subjects/group would be required to obtain significant effects on both MCCB and UPSA, providing guidance for continued clinical development in schizophrenia.

1. Introduction

Schizophrenia is a severe neuropsychiatric disorder associated with structural as well as neurochemical brain pathologies (Crespo-Facorro et al., 2009; Bhojraj et al., 2011; Johnstone et al., 2011). Although numerous compounds are currently under development to target neurochemical abnormalities in dopaminergic, glutamatergic, cholinergic and other brain systems, relatively few compounds directly target structural pathology or related genetic pathways. The present study investigates effects of the novel neurotrophic peptide davunetide in the treatment of cognitive impairments in schizophrenia.

Davunetide is an intranasal drug presently under development for treatment of Alzheimer's disease (AD) and progressive supranuclear palsy (PSP). Davunetide contains NAP, an 8 amino-acid peptide (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; NAPVSIPQ, MW = 824.9) fragment of the much larger Activity-Dependent Neuroprotective (ADNP) Protein (Gozes et al., 2009). NAP functions in animal models of AD and PSP by interacting with microtubules to promote neurite outgrowth (Gozes and Divinski, 2007; Vulih-Shultzman et al., 2007; Kushnir et al., 2008; Gozes et al., 2009). In schizophrenia, neurocognitive deficits are also reliably associated with dendritic impairments (Glantz and Lewis, 2000; Kamiya et al., 2005; Glantz et al., 2006; Goldman

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et al., 2009; Garey, 2010), suggesting potential relevance of this mechanism to schizophrenia as well as AD/PSP (Merenlender-Wagner et al., 2010). Furthermore, several genes associated with schizophrenia such as NRG1, Akt, and DISC1 function largely to modulate neurite outgrowth (Callicott et al., 2005; Kamiya et al., 2005; Shen et al., 2008; Young-Pearse et al., 2010; Johnstone et al., 2011; Lee et al., 2011), suggesting that this mechanism may target core neurogenetic disturbances in schizophrenia.

To be approved for treatment of cognition in schizophrenia, compounds must show efficacy not only on at least one domain of a standardized neuropsychological battery but also on a co-primary measure of functionally meaningful cognition (Buchanan et al., 2010). In the present study the MATRICS consensus cognitive battery (MCCB) (Nuechterlein et al., 2008) was used to assess neurocognition. Two potential co-primary measures of functionally meaningful cognition (Green et al., 2011) were also included: the UCSD Performance-based Skills Assessment (UPSA) and the Schizophrenia Cognition Rating Scale (Keefe et al., 2006).

In phase I studies, davunetide has been found to have a benign safety profile at doses of up to 30 mg/d. In the present study, two daily doses of davunetide were used: 5 mg (5 mg QD) and 30 mg (15 mg BID). The 5 mg dose was selected on the basis of preclinical pharmacology as corresponding most closely with the dose used in effective preclinical studies (Matsuoka et al., 2007). The 30 mg dose was selected as the maximum tested dose in phase 1 studies. For the present study, therefore, we hypothesized that the 5 mg dose would show greatest efficacy. In addition, the study was conducted within the framework of FDA-MATRICS-NIMH recommendations for clinical trial designs for potential neurocognitive enhancing agents (Buchanan et al., 2010).

As an initial pilot study of the mechanism, the present study was powered to detect only medium–large (0.5–0.8 SD) effect size changes and to determine overall treatment feasibility. However, even smaller magnitude changes may be clinically meaningful. For example, a d-score of .2 (small) is considered to represent the threshold for clinical detectability (Cohen, 1988; Rosenthal and Rosnow, 1991). Thus, in addition to significance a key goal of this study was to determine magnitude of change, expressed in effect size, in order to guide design of potential follow-up studies.

2. Methods

2.1. Subjects

Eighty six subjects were assessed for eligibility and 69 were randomized. Six were excluded prior to starting double-blind medication, leaving a sample of 63 subjects (41M/22F) who were enrolled across seven sites (Fig. 1). Groups were similar in age (placebo: 41.4 ± 10.4 yrs; 5 mg: 43.2 ± 10.5 yrs; 30 mg: 45.2 ± 8.2 yrs), education (placebo: 12.1 ± 2.7 yrs; 5 mg: 12.6 ± 2.2 yrs; 30 mg: 12.4 ± 2.7 yrs), and Wechsler Test of Adult Reading (WTAR) score (placebo: 26.1 ± 13.1; 5 mg: 32.0 ± 13.7; 30 mg: 28.6 ± 11.4).

Inclusion/exclusion criteria were implemented as proposed previously by the TURNS consortium (Buchanan et al., 2010). Briefly, clinically stable inpatients or outpatients age 18–60 were included. Inclusion criteria included treatment with second generation oral and/or first generation depot antipsychotics, average Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1961) hallucinatory behavior and unusual though content scores ≤5 and conceptual disorganization score ≤4, Simpson Angus Scale (SAS) (Simpson and Angus, 1970) total score ≤6, and Calgary Depression Rating Scale (CDS) (Addington et al., 1994) score ≤10. Patients had to be deemed capable of participating in neurocognitive testing and to have scores on the Wechsler Test of Adult Reading (Wechsler, 2001) ≥6.

Exclusion criteria included DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the last month, or a diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months. Subjects with a history of significant head injury/trauma or clinically significant medical or neurological disease were also excluded. Women of child bearing age were included only if using adequate birth control. Participation in a clinical trial of investigational medication within 60 days was also exclusionary.

Antipsychotic treatments were not changed during the trial. The most common medications were olanzapine (17/63, 27.0%), aripiprazole (15/63, 23.8%) and risperidone (11/63, 17.5%). Eleven (17.5%) patients were treated with injectable antipsychotics, including 5 with injectable risperidone. Three patients (2 placebo, 1 5 mg davunetide) were receiving lithium. All subjects gave informed consent. The trial was coordinated by the University of California, Los Angeles and approved by the UCLA IRB as well as by the IRB boards of the participating institutions (Clinicaltrials.gov registry #NCT00505765). The trial was conducted under FDA IND and oversight was provided by the NIMH Drug Safety and Monitoring Board.

2.2. Experimental drug protocol

Following screening, patients were entered into a 2-week stabilization phase during which baseline neuropsychological and symptom ratings were obtained. The primary outcome measure was the age- and sex-adjusted composite T score of the MCCB (Nuechterlein et al., 2008). MCCB T scores are standardized against a representative sample of the general population to have mean 50 and standard deviation 10. Secondary outcome measures included total scores from the UPSA (Heinrichs et al., 2006) and SCoRS (Keefe et al., 2006). Other assessments included the BPRS, Schedule for the Assessment of Negative Symptoms (Andreasen, 1984), Clinical Global Impression (CGI), CDRS, SAS and Abnormal Involuntary Movement Scale (Gharabawi et al., 2005).

Subjects who remained stable during the 2-week period were randomly assigned to low dose (5 mg), high dose (30 mg) intranasal (i.n.) davunetide or placebo. For low dose, 1 puff was administered daily (QD). For high dose (30 mg), 3 puffs were administered twice daily (BID). For the placebo group, one half were assigned to the low-dose protocol (1 puff QD) and one-half to the high dose (3 puffs BID). For statistical purposes, data were combined across placebo conditions. Medication was dispensed every two weeks. Compliance was determined by weight measure of returned insufflators.

Study duration was 12 weeks. MCCB, UPSA and SCoRS were obtained at weeks 6 and 12. For patients who terminated prior to study completion, results collected within 2 weeks of the next scheduled administration were used to assess outcome. Other clinical ratings and safety measures were obtained biweekly. An ECG was obtained at screening and study completion. Potential effects of nasal administration on olfaction were assessed using a 3-item version of the Smell Identification Test (Jackman and Doty, 2005). Potential for nasal irritation was assessed by visual inspection.

2.3. Statistical analyses

Analyses were performed using a mixed model analysis of covariance: follow-up score = baseline score + treatment + week + treatment × week. The primary outcome was estimated by the average adjusted treatment difference across week 6 and week 12 (main effect of treatment), with the treatment × week interaction term providing a post-hoc test for changes in treatment effects between weeks 6 and 12. All three pairwise contrasts between treatment groups were of interest. To control Type I error rates while performing 3 pairwise comparisons, Westfall's (1997) procedure was used (Westfall, 1997). Reliability of the MCCB across administrations was assessed using intraclass correlation coefficients (ICC).

Two-tailed statistics were used throughout. Values in text represent mean ± S.E. unless otherwise specified.