Piloting Treatment with IGF-1 in Phelan-McDermid Syndrome

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This project pilots the use of insulin-like growth factor-1 (IGF-1) as a novel treatment for Phelan-McDermid syndrome (PMS). IGF-1 is an FDA-approved (IND #121876), commercially available compound that crosses the blood-brain barrier and has beneficial effects on nerve cell communication and promoting mechanisms that underlie learning and memory.

Specific Aims

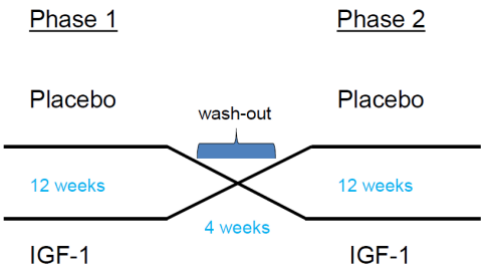
1) Evaluate safety, tolerability, and feasibility of IGF-1 vs. placebo in children with PMS targeting social withdrawal using the Aberrant Behavior Checklist – Social Withdrawal subscale (ABC-SW) as a primary outcome measure.

2) Evaluate safety, tolerability, and feasibility of IGF-1 vs. placebo targeting core and associated symptoms using measures of social, communicative, repetitive, sensory, and other problem behaviors.

Our working hypothesis was that IGF-1 would be safe, well tolerated, and associated with improvement on the ABC-SW subscale as compared to placebo.

Design

Participants were enrolled in two consecutive pilot studies. In each, treatment with IGF-1 or placebo was divided into two Phases (1 and 2). For both pilot studies, participants were randomly assigned to receive either IGF-1 or placebo for 12-weeks in Phase 1 and were then switched to the other treatment condition (Phase 2) after a four week wash-out period. We previously published positive results from the first pilot study [Kolevzon et al., Mol Autism. 2014 Dec 12;5(1):54] and the second pilot study was completed in September, 2016. Results from the second pilot study are presented herein, along with results combining the two pilot studies.



Participants

The first pilot study screened and enrolled nine children with PMS, and the second pilot study screened 11 patients and enrolled 10. Participants were required to have pathogenic deletions or mutations of the *SHANK3* gene for inclusion. Participants were between 5 and 14 years old (mean = 7.2; standard deviation = 2.8). Across both pilot studies, 9 participants were male and 10 were female. At baseline, all participants were at least moderately affected by social withdrawal according to the ABC-SW subscale: all scored at least one standard deviation above the mean as compared to a previously published sample of children with intellectual disability. Participants were on stable medication regimens for at least three months prior to enrollment.

Cases were excluded if any of the following criteria were applicable: (1) closed epiphyses; 2) active or suspected neoplasia; 3) intracranial hypertension; 4) hepatic insufficiency; 5) renal insufficiency; 6) cardiomegaly/valvulopathy; 7) history of allergy to IGF-1. None of the patients screened were excluded based on these criteria.

Drug Administration

IGF-1 is an aqueous solution for injection containing human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology. Based on the package insert, dose titration was initiated at 0.04 mg/kg twice daily by subcutaneous injection, and increased, as tolerated, every week by 0.04 mg/kg per dose to a maximum of 0.12 mg/kg twice daily. We aimed to reach the therapeutic dose as quickly as is safe and tolerated in order to allow maximum time for clinical improvement. Medication was administered twice daily with meals and glucose monitoring was performed by parents prior to each injection and at bedtime.

Study Visits

Measurements of social, communicative, repetitive, sensory, and other problem behaviors were taken at baseline and weeks 4, 8, and 12 of each treatment phase. Safety and tolerability was measured every two weeks throughout the trial during monitoring visits and phone calls.

Safety

Participants underwent comprehensive medical evaluations. Medical history, family history, physical and neurological examination, routine hematology and blood chemistry (including liver profile), bone X-ray for bone age, electrocardiography, and echocardiography were performed to determine eligibility for participation and repeated throughout the studies. Patients were monitored for safety at weeks 2, 4, 6, 8, 12 in both treatment phases (1 and 2) and then again four weeks after treatment completion.

There were no serious adverse events. Height, weight, cardiac, bone age, and laboratory monitoring did not show any evidence of clinically significant changes. The most common side effects of IGF-1 are related to its insulin-like activity and hypoglycemic risks. Training was conducted with parents at baseline visits for drawing finger stick blood glucose levels and monitoring for signs and symptoms of hypoglycemia. Training in administering subcutaneous injections was also performed. Hypoglycemia was defined as glucose <50 mg/dL. During the first pilot study (n=9), hypoglycemia occurred in 5/9 patients a total of 7 times while on IGF-1 and in 2/9 patients for a total of 3 times while on placebo. During the second pilot study (n=10), hypoglycemia occurred in 3/10 patients for a total of 4 times while on IGF-1 and in 3/10 patients for a total of 9 times while on placebo. With the exception of one occurrence in one participant, there were no clinical symptoms of hypoglycemia.

One patient discontinued after 4 weeks in Phase 2 of the first pilot study because of an ear infection and upper respiratory tract infection that required antibiotics and led to gastrointestinal symptoms, constipation, and decreased appetite. As a result, this patient was not able to sustain adequate glucose levels to continue treatment with IGF-1.

Data Analysis

All statistical analyses were conducted in the statistical package R. Before testing for drug efficacy, we first conducted analyses to test for potential bias in study design. First, we examined for potential carryover effects between Phase 1 and Phase 2 of the crossover trial. We then extended this methodology to examine for potential dataset effects to ensure the data from both the first published pilot trial (n=9) and the second pilot trial (n=10) could be combined without introducing significant bias. Collectively, the results of these tests suggest that data collection was highly standardized across all patients in both datasets and that the wash-out period was

successful in removing significant carry-over effects despite baseline differences in some measures across phases.

In terms of efficacy measurement, we tested for treatment × time interactions using mixed analysis of variance (ANOVA). Independent variables included between-subjects factor of treatment and within-subjects factor of time. We also tested for differences at week 12 between treatment groups (Phase 1 and 2) while controlling for baseline measurements. Using these methods, we analyzed three different combinations of our data: 1) new data from the second pilot study (n=10), 2) combined pilot studies (n=19) but using the only first phase of treatment (parallel group design), and 3) combined studies (n=19) with crossover analysis.

Results on the primary outcome measure, the ABC-SW, did not reach statistical significance in the second pilot study, combined dataset, or Phase 1 comparison. However, the overall magnitude of change of the ABC-SW while on IGF-1 in the second pilot study was comparable to that of the first pilot study (Kolevzon et al., 2014). The placebo response was higher in the second pilot study, thereby eliminating the statistical separation between groups (Fig 1). This may have occurred in part because the first pilot study results were published before completing the second pilot study, possibly biasing participants. While improvement in repetitive behaviors with IGF-1 was not statistically significant in the second pilot study, results were consistently in the direction of improvement and when we combined data from both pilot studies, we continue to see significant reductions on the Restricted Behavior subscale of the Repetitive Behavior Scale (Fig. 1).

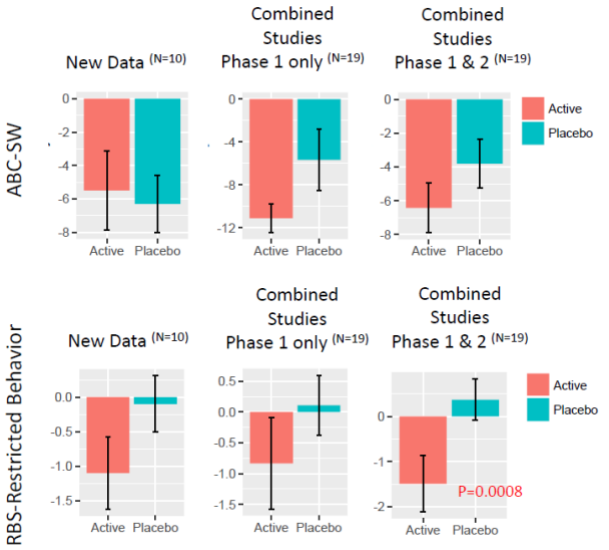


Figure 1: Change in scores at week 12 in ABC-SW and RBS Restricted Behavior

A new and important finding emerged with respect to hyperactivity as measured by the ABC. Hyperactivity is prominent in some of the patients. Improvement was enough to reach statistical significance (p=0.04) on the ABC-Hyperactivity subscale when analyzing data using the first phase only across both pilot studies. In all other analyses, including the first pilot study, trend level improvement was noted in this domain as well.

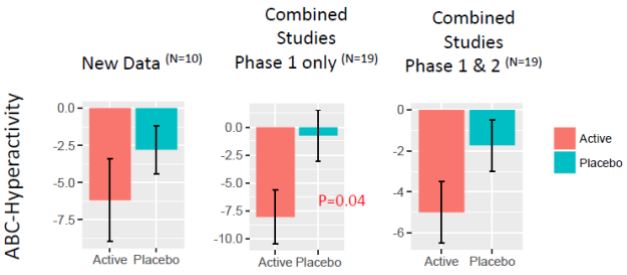


Figure 2: Change in scores at week 12 in ABC-Hyperactivity

In addition, we found improvement on two domains of the Sensory Profile, a validated measure of sensory reactivity. We previously have documented profound sensory under-responsiveness in PMS (Mieses et al., 2015). In the second pilot study, we found that the SP "sensory under-responsiveness/seeks sensation" domain, as well as the related "modulation related to body movement and position" domain improved significantly with IGF-1 as compared to placebo (Fig. 3). Though the direction of effects was similar in both sets of combined study analyses, results only reached statistical significance in the new data set.

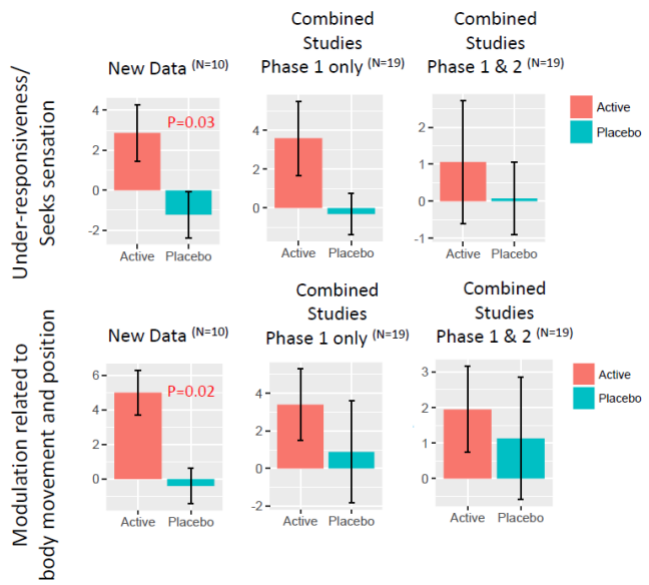


Figure 3: Change in scores at week 12 in Sensory Profile domains; lower scores on the Sensory Profile indicate greater deviation from the norm.

Conclusions

IGF-1 is safe over the course of 12 weeks of treatment and holds promise for treating symptoms of PMS, including social withdrawal, repetitive behaviors, sensory reactivity, and hyperactivity.

Future Directions

These data have been presented to Ipsen, the manufacturer of IGF-1, with the goal of obtaining free medication to allow us to include many more patients in future studies. However, we have secured additional funding to continue our IGF-1 program regardless of Ipsen's support. In addition, we have established a consortium of clinical sites across the U.S. to better understand the characteristics of PMS in order to select targets for treatment, study the natural history of the syndrome, and test the reliability of EEG biomarkers and clinical outcome measures across sites. Long term goals include the use EEG biomarkers to clarify IGF-1 dosing and stratify subgroups to predict treatment response in both PMS and autism spectrum disorder more broadly.