Angelman Treatments and Efficacy – Oral treatments trials

Early hopeful endeavors

MARK NESPECA, MD

RCHSD/UCSD

Methylation Trial I – NIH RDCRN

- Concept: epigenetic therapy - increased methylation could increase UBE3A production by altering antisense transcript that silences paternal UBE3A gene expression
- Agent: folate 15 mg + betaine 6 mg or 12 mg (weight based) daily
- WHO: # 57 enrolled – 5 mos- 14 yo: 48 completed I year; 2:1 Male:Female
- Randomized, Double Blind Placebo Controlled
- Outcome measures: evaluations at baseline and 1 yr: growth, exams, EEG, Bayley III, Vineland Adaptive Scale, Preschool Language Scale
- Results: no differences in BSID, VABS, PLS, growth, exams, seizure incidence or worsening; statistically sig difference in questionnaire with less hypermotor behavior in RX group
- Expected biochemical differences except for methylation assay

Peters S, et al. Am J Med Genet A . 2010 August ; 152A(8): 1994–2001

Methylation Trial II RDCRCN

- Concept: If we can increase methylation can we increase UBE3A expression and influence development safely
- Multiple methylation agents: folate, betaine, creatine, vitamin B12
- Who 5 mos – 5 yo (mean 34 months) all genotypes; M = F
- Open label – 90 enrolled 65 completed (variety of reasons for discontinuing)
- Measured outcome after one year: Bayley III, Vineland Adaptive Behavior Scale; Preschool Language Scale; Developmental Quotient
- Findings: no meaningful difference at one year compared to historical control of 16 children not treated with same evaluations; safe – labs ok; no difference in methylation assay
- Conclusion: above not effective in improving methylation assay or clinical developmental skill

Bird L et al: Am J Med Genet A . 2011 December ; 155(12): 2956–2963

Levodopa Trial

- Concept: AS mice suggested to have improved learning and LTP if phosphorylation of CamKII is reduced; levodopa treated mice improved motor performance; two adults with Parkinsonian tremor/rigidity improved with levodopa
- Med: levodopa 15 mg/kg/day (after preliminary dose ranging study)
- Randomized double-blind placebo controlled at 7 sites 4yo – 12 yo
- 78 recruited - (4 withdrew from RX 5 withdrew PBO group); 67 began therapy; 55 completed (withdrawals = both groups)
- Outcome Measures @ 1 yr: NO difference PBO vs. RX in BAYLEY III/Mullen, Vineland, Aberrant Behavior Checklist, Tremors (21 had tremors at inception), estimation of attention span, aggression or other aberrant behaviors
- Conclusion: though well tolerated 15mg/k/d showed no beneficial response on cognition, behavior, tremors, or estimate of attention

Tan WH, et al. Am J Med Genet A . 2018 May ; 176(5): 1099–1107

Minocycline Pilot

- Concept: minocycline alters dendritic spine configuration and improved synaptic plasticity (LTP) in mouse model of AS
- Med: minocycline 3 mg/k/d NTE 200 mg/day
- Open label single site: 25 AS persons 5 -13 yo (11 F 14 M) mean age 8 yo
- Duration of therapy: 8 weeks minocycline then 8 weeks off minocycline
- Outcome measures:

Primary = Change in raw scores on BSID III

Secondary = Vineland, Preschool Language Scale, (EEG score) (CGI)

- Findings: statistically sign increase in raw score of communication subtest, self direction, and fine motor on BSIDIII; statistically sig increase in VABSII receptive communication at week 8, PLS-IV auditory comprehension and total language at wk 16; no change in EEG scores or CGI
- Conclusion: future controlled studies and evaluation of long term effects needed before therapy with minocycline can be recommended

Grieco JC et al BMC Neurology 2014; 14:232

Minocycline Randomized Controlled

- Concept: "strong family treatment demand drove need to assess in controlled clinical trial"
- Med: minocycline 3mg/kg/day Maximum of 200 mg per day
- Randomized double-blind PBO A1: crossover arm 8week PBO> 8wk med B1: 8week med >8 wk PBO vs B2: 16 weeks minocycline
- Single Site: 32 individuals: ages 6-30 yo (mean 12 yo) (clinically matched) all Deletions except 2 UPD in RX arm
- Measures: Merrill-Palmer scale Developmental Index baseline and at 8 weeks after termination of RX arms namely week 24 ; CGI at 8, 16, 24 weeks; EEG qualitative pre and post
- Outcome: no difference in MP-R Developmental Index 8 wk, 16wk, or 24 wk ; @ 8 weeks higher CGI improvement *all groups* by parents only; no change in EEG; minocycline appears safe
- Conclusions: "results do not warrant the use of minocycline in AS"

Ruiz-Antoran B et al Orphanet J Rare Dis 2018; 13: 144

Gaboxadol **STARS** Trial unpublished

- Concept: GABA extrasynaptic receptor specific subunit agonist
- 78 pts randomized blinded to OVO1 15 mg/d or 10 mg/15 mg am/pm or placebo
- 12 weeks – primary objective evaluate safety and tolerability
- Secondary objective: reported effect on sleep, motor function, behavior
- CGI - I = Clinical Global Impression Improvement Scale
- Statistically significant improvement on CGI in treatment vs placebo group
- Conclusion: supports further development of OVO1 and use of CGI-1 as a study measure

Bird LM et al: AAN Annual Meeting May 4, 2019 Abstract