Advances in Parkinson's Disease

Clinical Research Update

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An uphill battle...

Clinical Trial Phases

MOTOR SYMPTOMS

QUOTE OF THE DAY

“All failure is failure to adapt. All success is successful adaptation”

• Tozadenant (SYN115) is an oral, selective adenosine A2A receptor antagonist that improves motor function in animal models of Parkinson’s disease.
• 2014 Phase 2B trial evaluated safety and efficacy of tozadenant as an adjunct to levodopa
• Dec 2017: terminated development of its Phase III due to deaths of five patients.
Apopomorphine for Off episodes

VS

- APL-130277 provided rapid improvement in patients with PD in the OFF state. The onset of clinical benefit appeared within 5-12 mins and was sustained over 90 mins.

- 22% of patients turned fully ON by 15 minutes and 59% by 30 minutes. At 30 and 90 minutes there was a 22 and 16-point improvement in the MDS-UPDRS Part III, respectively.

11 Dec 2017

- Sunovion completes a phase III trial in Parkinson's disease in Canada, USA and United Kingdom (Sublingual) (NCT02469090) (EudraCT2016-000636-18)

CTH-300: Pivotal Phase 3 Parkinson’s Disease Trial of APL-130277

- APL-130277, a fast-acting sublingual thin film for the treatment of debilitating OFF states in Parkinson’s disease (PD)

- The objective of the trial is to estimate the safety and efficacy of APL-130277 compared to a placebo

- All patient on levodopa +/- dopa agonist

- APL-130277 can convert patients from OFF episodes to ON states without the issues linked with subcutaneous administration of apomorphine.

Efficacy, Safety and Tolerability of PF-06649751 in Parkinson’s Disease Patients With Motor Fluctuations

- A 15-week, phase 2, double blind, randomized, placebo-controlled, dose ranging study to investigate the efficacy, safety and tolerability of PF-06649751

- Who: 98 PD subjects with motor fluctuations will be randomized to 5 treatment groups.

- Duration: 23 weeks total including a 30 day screening period, 15 week double blind treatment period, and an approximately 28 day follow-up period.

- Primary Outcome Measures: Change from baseline in daily OFF time

SAGE-217: tremor

- A Phase 2, Two-Part Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in Subjects With Parkinson’s Disease

- Second generation "neurosteroid", allopregnanolone

- Orally bioavailable steroidal derived GABA, positive allosteric modulator

- Part A of the study is an open-label design with dosing of Levodopa for 3 days followed by SAGE-217 for 4 days.

- Part B of the study is an open-label design with evening dosing of SAGE-217 for 7 days as an adjunct to antiparkinsonian agent(s).

- Primary outcomes:
  - Safety
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - PD tremor as assessed by changes in the MDS-UPDRS - Part II/III scores

New options for DBS

- FDA Approved: 2016

- FDA Approval anticipated
NON-MOTOR SYMPTOMS

ENT-01: constipation

Evaluation of Safety and Tolerability of ENT-01 for the Treatment of Parkinson's Disease Related Constipation (RASMET)

Chemical compounds originating in the dogfish shark, which can prevent alpha synuclein (αS) from accumulating within the nerves of the gastrointestinal (GI) tract.

- This is a Phase 1/2a study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of an orally-administered medication to relieve symptoms of constipation associated with Parkinson’s Disease.
- All subjects will receive the study drug during one of the observational periods of the study.

JZP-110: sleepiness

- JZP-110 is a selective dopamine-norepinephrine reuptake inhibitor
- This study is a 4-week, multicenter, randomized, double-blind, placebo-controlled, ascending dose, 4-period crossover study designed to evaluate the safety, tolerability, efficacy, and PK of JZP-110 [(R)-2-amino-3-phenylpropylcarbamate Hydrochloride]
- Dosage will be 75, 150, and 300 mg in the treatment of excessive sleepiness in adult subjects with idiopathic PD.
- Primary outcome:
  - Safety as assessed by the incidence of treatment emergent adverse events up until the last visit at week 5
  - Maintenance of Wakefulness Test (MWT)
- Secondary outcomes:
  - Epworth Sleepiness Scale (ESS)

A Non-Motor & Non-Dopaminergic Approach?

Serotonin's role in PD-Dementia

Phase II: Proof of Concept Study to Evaluate Its Safety, Tolerability and Efficacy in Parkinson’s Disease Dementia

This study includes a Screening Period of up to 6 weeks, a 16 week Treatment Period, and a 2 week Safety Follow Up Period.

Inclusion Criteria:
- Parkinson’s Disease Dementia
- Patient has a routine caregiver
- Taking a stable cholinesterase inhibitor.
- Patient has a Montreal Cognitive Assessment (MoCA) 10-23 inclusive

SYN120 Doses to be Administered: 20 mg QD (1 week titration), 50 mg QD (1 week titration), 100 mg QD (14 weeks of maintenance).

Neuroprotective Strategies
Anti-Anti-Synuclein Antibodies?

- BIIB054 is a human recombinant monoclonal antibody targeting alpha-Synuclein.
- Transmission of α-syn pathology may also contribute to disease progression.
- Immunotherapy against α-syn is thus a promising therapeutic approach for slowing disease progression.
- A Phase I Randomized, Double-Blinded, Placebo-Controlled Single-Ascending Dose Study. Phase II expected to begin enrollment soon.

Who: Both Healthy subjects and subjects with Early Parkinson's Disease <3 years from diagnosis.

The primary objective of the study is to evaluate the safety and tolerability of a range of single BIIB054 doses.

Inosine: Multicenter, Randomized, Double-blind, Placebo-controlled, Phase III Trial

- Estimated Enrollment: 270
- Study Start Date: June 2016
- Estimated Study Completion Date: August 2020

- A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial to determine whether oral inosine dosed to moderately elevate serum urate levels (from ≤5.7 mg/dL to 7.1-8.0 mg/dL) over 2 years slows clinical decline in early PD.
- The primary outcome of the trial is rate of change in MDS-UPDRS I-III total score over 24 months.
- Who:
  - Age 30 or older at the time of PD diagnosis.
  - Diagnosis of PD made within 3 years of first screening visit.

2014 Phase II Conclusions and Relevance: Inosine was generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. The findings support advancing to more definitive development of inosine as a potential disease-modifying therapy for PD.

Single-Ascending Dose Study of BIIB054 in Healthy Participants and Early Parkinson’s Disease

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AAV2-hAADC (adeno-associated virus type 2-human Aromatic l-amino acid decarboxylase)

- AADC is the rate-limiting step (i.e. most important step) for the conversion of L-Dopa to dopamine (DA).
- Loss of AADC (Ichinose et al., 1994) may be responsible for the decreasing effect of long-term L-Dopa therapy.
- Use of a gene therapy viral vector encoding AADC is now possible to restore endogenous AADC.
- A Phase II study has demonstrated that this process appears to be safe in PD patients.

AAV2-hAADC (continued)

- An Open-label Safety and Efficacy Study of VY-AADC01
- Ten patients with moderately advanced PD received randomized to low or a high dose of AAV2-hAADC vector.
- An annual positron emission tomography (PET) to evaluate AADC expression, and the Unified Parkinson's Disease Rating Scale (UPDRS)
  - PET scan suggests changes persist in the brain for over 4 years in both dose groups.
  - The UPDRS in all patients off medication for 12 hr improved in the first 12 months, but displayed a slow deterioration in subsequent years.

Glutathione – Antioxidant Neuroprotective Therapy?

- Antioxidant levels decrease with age
  - Lower glutathione is associated with more severe PD
- Existing available forms:
  - Pill – Very poor gut absorption
  - Intranasal – experimental
  - Intravenous - experimental

Diabetes drugs for Parkinson’s disease??

- Diabetes Types 1, 2, and 3?

Insulin and its role in the brain

A complex brain signaler, insulin is involved in:
- cell growth and survival
- neurotransmission and waste removal
- central regulation of metabolism
- the hypothalamus and appetite
- synaptic plasticity
- neuroprotective functions

Importantly insulin can readily cross the blood-brain barrier

Adapted from Morris (2014) Neuroscience and Kleinridders (2015) PNAS
The case for Parkinson’s Disease as type 3 diabetes

Insulin resistance (IR) leads to the development of Diabetes which increases the risk of developing Parkinson’s disease

IR and Diabetes share pathologic hallmarks of Parkinson’s Disease
- Altered dopamine function
- Alpha-synuclein
- Mitochondrial dysfunction
- Oxidative stress

IR and diabetes worsens motor and non-motor features of PD in humans and animal models

Therapies (such as diet, exercise, and antidiabetic drugs) that improve IR can improve PD symptoms...

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Does an energy problem underlie Parkinson’s disease?

- Aging is a key pathologic driver of Parkinson’s Disease
- Aging is accelerated by a high level of energy intake and is slowed by energy restriction.
  This has been seen from worms and flies, to rodents and monkeys...


Mitochondria and Oxidative Stress

- The two main events behind the death of the dopamine producing brain cells in PD are:
  - Failure of the mitochondria
  - Oxidative stress (formation of free radicals)
- The most intensively studied PD related genetic mutations (PARK1 and LRRK2, etc) affect a-synuclein and impair mitochondrial function, i.e. they cause an energy problem for the brain


Insulin Resistance and Mitochondria

- IR and type 2 diabetes are associated with mitochondrial dysfunction in muscle and liver
- IR in the brain is also associated with mitochondrial dysfunction
- Obesity-induced IR has also been shown to alter mitochondrial function, specifically in the hypothalamus
- The hypothalamus controls appetite which can create a vicious cycle

Insulin Resistance causes mitochondrial dysfunction

Adapted from Kleinridders (2015)/PNAS

Insulin and Dopamine

Insulin is central to Diabetes

Dopamine is central to Parkinson’s

Insulin and Dopamine are surprisingly connected in the brain

Insulin receptors are present in the substantia nigra
Cell death in this region reduces number of insulin receptors, impairing glucose uptake

Animal studies show PD drugs can influence insulin production, insulin resistance, and blood sugar control

Insulin delivered directly to the brain increased the amounts of Dopamine transporter activity in the Substantia Nigra

Low insulin resulting from induced diabetes has been shown to decrease brain Dopamine concentrations

Insulin: Implicated in the production of alpha-synuclein...

Shared dysregulated pathways lead to Parkinson's disease and diabetes

The case for Parkinson's Disease as type 3 diabetes

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IR and diabetes worsens motor and non-motor features of PD in humans and animal models.

Therapies (such as diet, exercise, and antidiabetic drugs) that improve IR can improve PD symptoms...

How Prevalent is Insulin Resistance in Parkinsons?

Abstract: High prevalence of undiagnosed insulin resistance in non-diabetic people with Parkinson's disease

Objective: To study the prevalence of undiagnosed insulin resistance (IR) in people with Parkinson's disease (PD)

Methods: 85 idiopathic PD people attending the movement disorders clinic at Cedars-Sinai Medical Center were offered testing for fasting insulin and glucose.
- HOMA index was used to identify those with IR.
- Body Mass Index (BMI) and co-morbid diagnosis of diabetes mellitus were noted.

It certainly seems so...

Diabetes and the Risk of Developing Parkinson’s Disease in Denmark

- Several studies have found that diabetes is strongly associated with PD in humans
- A Danish study used the Danish Hospital Register records to identify 1,931 patients with a first-time diagnosis of PD between 2001-2006 and compared them with healthy controls.
- Having diabetes was associated with a 36% increased risk of developing PD
Diabetes increases risk for Parkinson's disease

The case for Parkinson's Disease as type 3 diabetes

Insulin Resistance is associated with more severe PD

The case for Parkinson's Disease as type 3 diabetes

Low calorie diet protects against MPTP lesioning in Monkeys

High fat diet leads to insulin resistance and DA dysfunction

- In a study of rhesus monkeys, one group was maintained on the usual diet and the calorie intake of another group was reduced by 30%.
- After 6 months all monkeys were injected with MPTP
- Monkeys in the calorie restriction group exhibited less motor deficits and higher levels of dopamine, BDNF and GDNF in their striatum.
- This has been shown in other animal models as well

- Rats fed a high fat diet had reduced Dopamine release
- Decreased Dopamine release was more evident in animals with a greater degree of IR (as measured by HOMA-IR)
- They had lost the capacity to combat oxidative stress
Unfortunately, diet matters in humans too...

- Individuals with a high calorie intake are thought to be at increased risk of PD.

How about intermittent fasting?
- No interventional trials of intermittent fasting in PD patients.

- Intermittent fasting induces the expression of protein chaperones (HSP70 and GRP78), the antioxidant enzyme heme oxygenase 1, and the neurotrophic factors BDNF and fibroblast growth factor 2 in several brain regions.

- In addition, intermittent fasting increases levels of ketone bodies, which are known to protect neurons against excitotoxic and metabolic stress.

Adapted from Mattson MP (2014) Journal of Parkinson’s Disease

Exercise

Exercise can prevent or reverse IR and Diabetes and is also neuroprotective for PD

Exercise – a true panacea?

- Exercise has been reported to delay disease onset and slow progression in mouse models of PD.

- Exercise also increases the number of the dopamine receptors in neurons in MPTP-treated mice.

- Exercise resulted in increased brain blood vessel density in MPTP-treated mice, suggesting a potential role in angiogenesis (blood vessel growth).

Adapted from Mattson MP (2014) Journal of Parkinson’s Disease

Can exercise prevent Parkinson’s?

- Of 213,701 participants in the NIH-AARP Diet and Health Study, individuals who engaged in exercise from the ages of 35–39 had a 40% lower risk of developing PD compared to those who were relatively inactive.

- In another study of PD patients, a three times weekly intensive 60 minute exercise program resulted in significant improvements in mobility and balance.

Overall, data suggest that regular exercise can reduce the risk of PD modestly, and that exercise programs improve symptoms in PD patients.

Adapted from Mattson MP (2014) Journal of Parkinson’s Disease

The next treatment frontier?

Exenatide and the treatment of patients with Parkinson's disease

- Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson’s Disease

- At 60 weeks, off-medication scores on part 3 of the MDS-UPDRS had improved by 1·0 points (95% CI −2·6 to 0·7) in the exenatide group and worsened by 2·1 points (−0·6 to 4·8) in the placebo group, an adjusted mean difference of −3·5 points (−6·7 to −0·3; p=0·0318).

- Injection site reactions and gastrointestinal symptoms were common adverse events in both groups.

Adapted from J Clin Invest. 2013 Jan;123(1):273-86

Double Blind Placebo Controlled Trial of Exenatide

Adapted from Mattson MP (2014) Journal of Parkinson’s Disease
Liraglutide: A More Powerful GLP-1 Agonist

Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study

First trial of Liraglutide in PD

The trial has begun at Cedars-Sinai Medical Center in partnership with NovoNordisk and the Cure Parkinson's Trust, UK.

A Phase II, Randomized, Double-blind, Placebo-controlled Trial of Liraglutide in Parkinson's Disease

- This study will test a new symptomatic and possibly disease-modifying therapy, while shedding light on the role of insulin resistance in the pathogenesis of PD.
- We will randomize 57 patients with a diagnosis of idiopathic PD to receive once daily injections of liraglutide (1.2 or 1.8 mg), or placebo, in a 2:1 study design.

Safety and Efficacy of Liraglutide in Parkinson's Disease

NCT02953665

- Primary Outcome Measures:
  - Motor Function [Time Frame: 54 weeks]
    - Determined by the change in the motor (Part III) Movement Disorders Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) score in the active treatment arm versus placebo between baseline, 28 and 54 week visit.
  - Non-Motor Function [Time Frame: 54 weeks]
    - Determined by the change in the Non-Motor Symptoms Scale (NMSS) score in the active treatment arm versus placebo between baseline, 28 and 54 week visit.
  - Cognitive Function [Time Frame: 54 weeks]
    - Determined by the change in the Mattis Dementia Rating Scale (MADRS-2) score in the active treatment arm versus placebo between baseline, 28 and 54 week visit.

Far horizon: Stem cell therapy

More Questions than answers:
- What type of stem cell do we use?
- How do we introduce the cells to the brain correctly?
- How do we encourage the cells to join or repair existing cell networks?
- How will we manage safety concerns?
- How long will the effects (if any) last?