A Phase 1 Clinical Study of the Retinoid X Receptor (RXR) Selective Agonist IRX4204 in Patients with Early Parkinson's Disease (PD)

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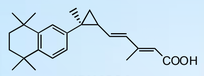
ABSTRACT

OBJECTIVES: To evaluate the safety, tolerability, and effects on dopamine transporter binding (DAT), UPDRS Total and Motor Score, of short term administration of IRX4204 to patients with early PD.
BACKGROUND: IRX4204 is a highly selective and potent agonist of the RXR nuclear receptors, and of RXR-Nurr1 and RXR-Nur77 heterodimers. IRX4204 and other RXR agonists previously have been reported to promote dopaminergic neuron survival and functions in vitro, and to be effective in vivo in a 6-OH induced rat model of PD.
DESIGN: This study was a single center, open-label clinical trial. IRX4204 was administered orally, once daily, at 5, 10, or 20 mg/day, for up to 30 days. Three cohorts of 5 early PD patients were enrolled. Patients were evaluated for safety, UPDRS, and DAT binding using [123I]β-CIT SPECT.
RESULTS: Few adverse events, all non-serious, were observed. Safety laboratory side effects, including known RXR agonist class related reductions in TSH, T4, and circulating leukocytes; and elevations of circulating triglycerides, occurred at all dose levels. Treatment was suspended in the 20 mg/day cohort for decreased leukocytes; and in one patient in the 10 mg/day cohort for elevated triglycerides. No effect on DAT expression was observed by SPECT. There was a trend toward reduction of UPDRS total scores by 4.6 (SD 3.9).
CONCLUSIONS: IRX4204 was safe and well tolerated by early PD patients at 5 and 10 mg/day for 30 days. No short-term effect on DAT binding was observed by SPECT. There was a trend towards improvements in UPDRS in this open label study. More definitive assessment of UPDRS change after treatment with IRX4204, will require future blinded, controlled clinical trials. These are the first human clinical data to support RXR agonists may be effective for treatment of PD.

OBJECTIVES

To evaluate the safety, tolerability, and effects on dopamine transporter binding (DAT), UPDRS Total and Motor Score, of short term administration of IRX4204 to patients with early PD.

Figure 1



IRX4204

3,7-Dimethyl-6(S),7(S)-methano,7-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl] 2(E), 4(E) heptadienoic acid

Molecular Formula $C_{24}H_{32}O_2$

Molecular Weight 352.51

BACKGROUND

IRX4204 is a second-generation Retinoid X Receptor (RXR)-specific agonist (rexinoid). By binding and activating RXR nuclear receptors, rexinoids regulate differentiation, proliferation and survival of neurons and oligodendrocytes, in normal tissue development, in animal models of various neurodegenerative diseases, and possibly in humans.

Figure 1 shows the molecular structure of IRX4204. Although the compound has two chiral centers, it is synthesized as an optically pure isomer. Figure 2 shows that IRX4204 is a potent agonist of RXR nuclear receptors in transactivation assays, with EC_{50} less than 1 nM, and EC_{90} of approximately 1 nM for each of the three RXR isoforms. Figure 3 shows that IRX4204 is at least 100 fold more potent as an RXR agonist, for all 3 RXR isoforms, than bexarotene, a first generation less selective RXR agonist approved by the FDA for treatment of T-cell lymphoma. Bexarotene has been reported to be active in animal models of PD, AD, MS, ALS, and ischemic stroke.

We have previously reported preclinical studies with IRX4204 demonstrating activity in the 6-hydroxy dopamine induced model of PD in rats (Wang J, et al, Oncotarget, 2016). In those studies, orally administered IRX4204 activated increased in vivo expression of Nurr1 downstream genes, including DAT and DDC; improved motor functions; and preserved tyrosine hydroxylase midbrain neurons on histopathology. We have reported previously (Chandraratna R et al, Am J Tranl Res, 2016), and in other abstracts in this conference, that IRX4204 also is active in preclinical models of MS, and in models of AD. We now report our first clinical experience with IRX4204 in patients with a neurodegenerative disease, i.e. Parkinson's disease.

Figure 2
RXR and RAR Transactivation of IRX4204

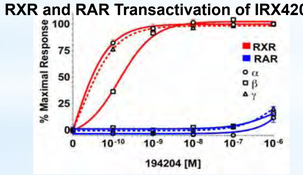
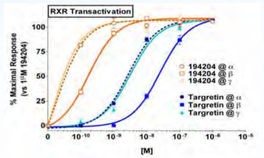


Figure 3
RXR Transactivation of IRX4204 vs bexarotene



DESIGN

The study is an open-label, non-randomized, non-controlled assessment of safety, and potential activity of IRX4204 for the treatment of Parkinson's disease.

Ethics Review and Informed Consent: The protocol was IRB-approved and was conducted under a company-sponsored US IND. All patients were required to sign an IRB approved informed consent before participating in any study activities.

Dosing: Patients were administered IRX4204 at a fixed dose levels of 5, 10, or 20 mg/day, formulated in gelatin capsules. Patients were to be dosed for a total of 30 days. Three cohorts, each of 5 early PD patients were enrolled.

Inclusion/Exclusion Criteria: Fifteen early PD patients who were medically stable and met the inclusion criteria, and did not meet any of the exclusion criteria, were enrolled into the study. Major inclusion criteria were: 40-80 years of age; clinical diagnosis of PD based on the UK Brain Bank Criteria; Hoehn and Yahr stage < 3; may be treated with PD symptomatic therapy on a stable dose for at least 30 days prior to the Screening Visit. Dose levels of PD symptomatic therapies were required to remain stable through the patient's participation in the study, unless a change of dose level is indicated because of adverse events; willing and able to provide informed consent; non-child bearing potential. Major exclusion criteria were any form of parkinsonism other than idiopathic PD; experiencing motor fluctuations (end of dose wearing off or dyskinesias) reflective of later stage PD; dementia or significant cognitive dysfunction; clinically significant abnormal laboratory value and/or clinically significant unstable medical or psychiatric illness.

Assessments: Safety assessments included physical examinations, recording of adverse events, clinical laboratories including CBCs, chemistry profiles, lipids, thyroid hormone and TSH levels, and ECGs were performed.

UPDRS was assessed at screening, pretreatment baseline, and at week 2, and week 4.

DAT binding was assessed by pre-treatment and end of treatment [123I]β-CIT SPECT.

Author Disclosure Information: **M.E. Sanders:** ; Chief Executive Officer, Io Therapeutics, Inc., No, Io Therapeutics, Inc., No, Io Therapeutics, Inc., Io Therapeutics, Inc., Io Therapeutics, Inc. **R. Chandraratna:** ; President and Chief Scientific Officer of Io Therapeutics, Inc., Stock in Io Therapeutics, Inc. **K. Marek:** ; Dr Marek received compensation as a consultant for Molecular Neuroimaging, GE healthcare, Piramal, Eli Lilly, Merck, Roche, Pronetha, Novartis, US World Meds, and nLife.. **D. Jennings:** None.

RESULTS

Tolerability and Safety
Few adverse events, all non-serious, were observed.
Safety laboratory side effects, including known RXR agonist class related reductions in TSH, T4, and circulating leukocytes; and elevations of circulating triglycerides, occurred at all dose levels. Profound suppression of circulating TSH, and associated reduction of T4 to hypothyroid levels was observed in the 20 mg/day group, a known effect of RXR agonism. Lower dose levels demonstrated less suppression of TSH in a dose response fashion.

Mean % Change in Plasma TSH Levels Pretreatment to Week 2

Dose	% Change
20 mg/day	-98.8%
10 mg/day	-36.6%
5 mg/day	-28.9%

Treatment was suspended in the 20 mg/day cohort at two weeks for decreases in circulating leukocytes, which were rapidly reversible upon cessation of study drug. One patient in the 10 mg/day cohort had treatment discontinued for asymptomatic elevated triglycerides of 777 mg/dL .

Efficacy Assessments
In this short term study, no effect on DAT expression was observed comparing baseline and end of study [123I]β-CIT SPECT.

There was a trend toward reduction of UPDRS and total motor scores in this open label study. Decrease in UPDRS and total motor scores was greatest in the lowest dose group (5 mg/day).

Mean % Change in Total Motor Score and UPDRS Pretreatment to Week 2

Dose	% Change Total Motor Score	% Change UPDRS
20 mg/day	-14.5%	- 6.6%
10 mg/day	-11.7%	-13.6%
5 mg/day	-31.4%	-18.7%

CONCLUSIONS

IRX4204 was safe and well tolerated by early PD patients at 5 and 10 mg/day for 30 days.

No short-term effect on DAT binding was observed by SPECT.

There was a trend towards improvements in Total Motor Scores and UPDRS in this open label study. The greatest improvements were observed in patients treated with the lowest dose of IRX4204, who also had the least reduction in TSH and circulating thyroid hormone. More definitive assessment of Total Motor and UPDRS change after treatment with IRX4204 will require future blinded, controlled clinical trials. Supplementation with thyroid hormone may be critical for optimal treatment effects of RXR agonists for neurodegenerative diseases.

These are the first human clinical data to support that RXR agonists may be effective for treatment of PD.