PPARδ Agonist Mavodelpar (REN001) Improves Mitochondrial Function in Skeletal Muscle: an Investigational Treatment for Primary Mitochondrial Myopathies*

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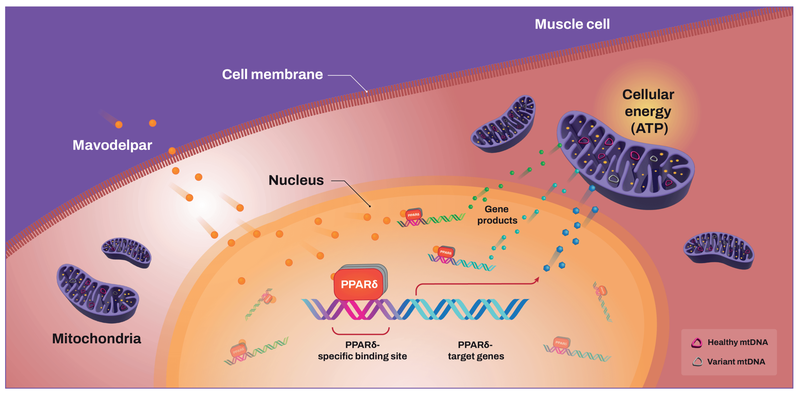
BACKGROUND

- Peroxisome proliferator–activated receptor delta (PPARδ) is a nuclear transcription factor that transactivates genes required for mitochondrial respiration and oxidative metabolism (Figure 1)[1-3]
- In skeletal muscle, PPARδ agonists enhance fatty acid oxidation (FAO) and mitochondrial biogenesis[1-5]
- Primary mitochondrial myopathies (PMM), characterized by skeletal muscle weakness and fatigue due to dysfunctional mitochondria, cause impaired mobility and exercise intolerance[4,6]
- PPARδ agonists upregulate the expression of genes involved in mitochondrial function and increase muscle endurance[2,5,7]
- PPARδ agonists may be attractive candidates for treatment of PMM[2,5,7]
- Mavodelpar (REN001) is a novel, investigational, orally administered, potent, and selective full agonist of PPARδ that has been optimized for peripheral tissue distribution and once-daily dosing. It is currently being investigated in clinical trials for PMM

Figure 1. Mechanism of Action of PPARδ Agonists



Abbreviations: ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; PPARδ, peroxisome proliferator–activated receptor delta.

OBJECTIVE

- The objective of the analyses described here is to establish the potential utility of PPARδ agonist mavodelpar for PMM

METHODS

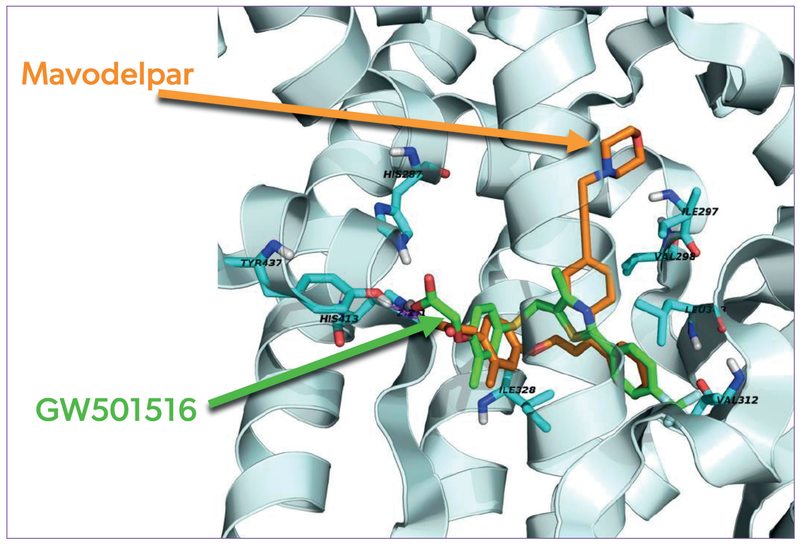
- Computational modeling, in vitro, and in vivo studies were used to establish the potency and selectivity of mavodelpar activation of PPARδ and transactivation of genes associated with regulation of mitochondrial function in skeletal muscle
  - For computational modeling, mavodelpar was docked in PPARδ using a high-resolution crystal structure of PPARδ complexed with the less selective agonist GW501516
  - Mavodelpar was tested for specificity and potency via in vitro transactivation assays on human, mouse, rat, and cynomolgus monkey PPAR receptors. These transactivation assays were performed by transfecting eukaryotic cells in culture with 2 DNA plasmid vectors. One vector encodes the PPAR receptor protein whereas the other harbors a reporter gene engineered to be under transcriptional control by the expressed PPAR protein
  - FAO assays were performed in rat (L6) and human (XM5) muscle cell lines measuring oxidation of fatty acid (FA) ^{3}H-Palmitate substrate
  - Glucose oxidation was measured in the same way as FAO with the exception that the tritiated palmitate was replaced by 10 µCi/ml [5-^{3}H]-D-glucose
  - Male C57BL/6 mice were administered an oral dose of mavodelpar at 30 mg/kg or vehicle, once daily for 7 consecutive days. Four hours following the final dose administration on Day 7, all mice were euthanized. Samples of quadriceps muscle were dissected for analysis of messenger RNA (mRNA) expression patterns of several well-know PPARδ-regulated genes and pathways, including those important for 1) FA transport into mitochondria (carnitine palmitoyltransferase 1B [*CPT1B*]); 2) oxidative phosphorylation (pyruvate dehydrogenase kinase 4 [*PDK4*]); and 3) mitochondrial biogenesis (PPAR gamma coactivating factor 1 alpha [*PGC-1α*])
  - Male Sprague-Dawley rats were administered an oral dose of mavodelpar at 30 mg/kg or vehicle, once daily for 6 consecutive days. Four hours following the final dose administration on Day 6, all animals were euthanized, and samples of quadriceps muscle were dissected and processed for angiopoietin-like 4 (*ANGPTL4*) mRNA expression analysis

RESULTS

Computational modeling

- Computational modeling demonstrates that mavodelpar fits selectively into the binding pocket of PPARδ (Figure 2)
- When mavodelpar was docked in PPARδ using a high-resolution crystal structure of PPARδ, the docked pose of mavodelpar showed features in common with the PPARδ agonist GW501516 crystallographic binding model plus additional protein contacts

Figure 2. Binding of Mavodelpar and GW501516 in PPARδ



Overlay of docked pose of mavodelpar (orange) in PPARδ (aqua) with crystallographic binding mode of PPARδ agonists GW501516 (green), showing the unique mavodelpar sidechain in the upper right.

Abbreviation: PPARδ, peroxisome proliferator–activated receptor delta.

Nuclear transactivation assays

- Mavodelpar was tested on all 3 human, murine, and cynomolgus monkey PPAR subtypes (PPARα, PPARγ, and PPARδ)
- Mavodelpar was a potent and selective full agonist of human and cynomolgus monkey PPARδ in recombinant cell lines (half maximal effect concentration [EC_{50}] = 31 nM and 6.6 nM, respectively) (Table 1)

Table 1. In Vitro Transactivation Data for Mavodelpar in Human, Rodent, and Cynomolgus Monkey PPAR Receptors

Species	N	PPARδ	PPARγ	PPARα
Human	4	EC_{50} (nM): 31±3 %Max: 301±8	EC_{50} (nM): >10,000	EC_{50} (nM): >10,000
Murine	4	EC_{50} (nM): 240±40 %Max: 147±65	EC_{50} (nM): >10,000 %Max: >14	EC_{50} (nM): >10,000 %Max: NA
Rat	4	EC_{50} (nM): 500±7 %Max: 148±12	NT	NT
Cynomolgus monkey	4	EC_{50} (nM): 6.6	EC_{50} (nM): >1000	EC_{50} (nM): >1000

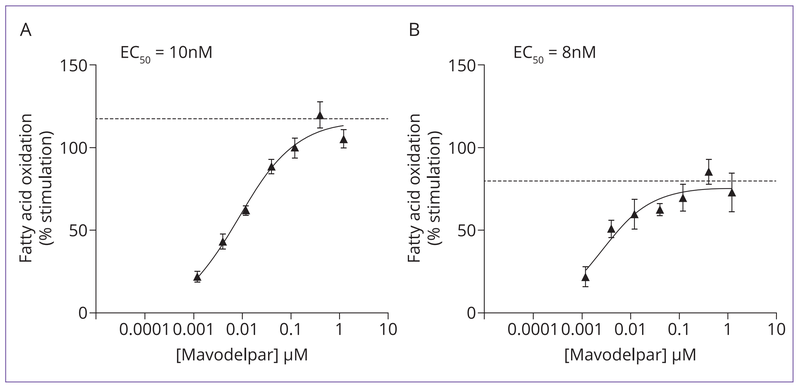
Abbreviations: EC_{50}, half maximal effect concentration; Max, maximum; N, number of replicates; NA, not applicable; NT, not tested; PPAR, peroxisome proliferator–activated receptor.

Mavodelpar, a potent and selective PPARδ agonist that increases expression of PPARδ-regulated genes for fatty acid metabolism, oxidative phosphorylation, and mitochondrial biogenesis in skeletal muscle, is being evaluated as a potential treatment for PMM.*

In vitro FAO in rat and human muscle cell lines

- Mavodelpar increases FAO in rat and human skeletal muscle cell lines in a dose-dependent manner (Figure 3)
  - No significant effect on glycolysis was detected (data not shown)

Figure 3. Dose-Response Curves for Mavodelpar on Fatty Acid Oxidation in Rat L6 (panel A) and in Human XM5 (panel B) Muscle Cell Lines



Abbreviation: EC_{50}, half maximal effect concentration.

In vivo gene expression evaluation in mouse muscle

- After oral dosing of mavodelpar in mice, mean (± standard error of the mean [SEM]) skeletal muscle mRNA expression of *CPT1B*, *PGC-1α*, *PDK4*, and mitochondrial uncoupling protein 3 (*UCP3*) were 1.35±0.15, 1.65±0.19, 1.88±0.17, and 2.29±0.27-fold over vehicle, respectively (Table 2)

Table 2. Gene Expression in Mice After 7 Days of Treatment With Mavodelpar

			Fold-Change Over Vehicle	
Gene	Name	Gene Category	Mean	SEM
PGC-1α	PPARγ coactivating factor 1α	Transcriptional cofactor	1.65	0.19
CPT1B	Carnitine palmitoyltransferase 1B	Fatty acid metabolism	1.35	0.15
PDK4	Pyruvate dehydrogenase kinase 4	Fatty acid metabolism	1.88	0.17
UCP3	Mitochondrial uncoupling protein 3	Fatty acid metabolism	2.29	0.27

Abbreviation: SEM, standard error of the mean.

In vivo gene expression evaluation in rat muscle

- ANGPTL4 increases the maximum mitochondrial oxidative capacity in skeletal muscle through adenosine monophosphate (AMP)-activated protein kinase activation[7]
- In rats, skeletal muscle mRNA expression of *ANGPTL4* increased by 5.5±2.7-fold (mean ± standard deviation) over vehicle (1.38±1.3) in mavodelpar-treated animals (P<0.01)

DISCUSSION AND CONCLUSIONS

- Mavodelpar is a potent and selective PPARδ agonist
- Mavodelpar activation of PPARδ results in increased transcription of genes involved in mitochondrial biogenesis, FAO, and energy production in the form of adenosine triphosphate (ATP)
- An increased rate of FAO in muscle is believed to be a central part of the mechanism by which PPARδ activation improves exercise capacity in mice; mavodelpar significantly and dose-dependently increased FAO in rat and human muscle cell lines[2,8,9]
- Rather than generally increasing energy consumption, PPARδ activation with mavodelpar specifically increased FAO since no effect on glucose oxidation was observed
- Mavodelpar is being evaluated in clinical trials as a potential treatment for PMM*

DISCLOSURES

John W. Adams is an employee of Reneo Pharmaceuticals, Inc. and owns stock in the company. Meg McCarrick is a former consultant for Reneo Pharmaceuticals, Inc., and is currently an employee of Plexium, Inc. Colin O'Carroll is a former employee of Reneo Pharmaceuticals, Inc., and is currently an employee of Acadia Pharmaceuticals, Inc.

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SCAN ME

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*Mavodelpar is an investigational treatment not yet approved by any regulatory agency.

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