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TITLE: Inner and Outer Nuclear Layer Atrophy of the Retina as Novel and Distinguishing Biomarkers for Defining and Tracking Progressive Multiple Sclerosis

PRINCIPAL INVESTIGATOR: Dr. Shiv Saidha

CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

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14. ABSTRACT Progressive multiple sclerosis (PMS) is a form of multiple sclerosis (MS) characterized by steady and gradual accumulation of disability. Optical coherence tomography (OCT) has emerged as a complementary tool to magnetic resonance imaging (MRI) with utility for tracking neurodegeneration in relapsing-remitting MS (RRMS). However, PMS is less well understood, hindering development of effective treatments. Herein, this project seeks to address these gaps by confirming and validating the predominance of INL (inner nuclear layer) and ONL (outer nuclear layer) retinal atrophy in PMS and evaluate their utility for the development of more specific PMS outcomes, and shedding light on the pathobiology of PMS. This project uses OCT and other data acquired from the SPRINT-MS trial, a 96-week, randomized, double-blind, placebo controlled study of the phosphodiesterase inhibitor ibudilast in 255 primary and secondary PMS patients. The project's first year milestones have been successfully completed, including all steps in the process of regulatory approval and data transfer. Work towards year two milestones of year two, specifically OCT segmentation, is underway. This is the first step towards obtaining high quality data to study whether rates of atrophy of ganglion cell + inner plexiform layer (GCIPL), INL and ONL are lower in ibudilast versus placebo treated PMS patients, and the relationships of OCT captured treatment effects with a broad spectrum of clinical and MRI measures.									
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems	6
6. Products	6
7. Participants & Other Collaborating Organizations	6
8. Special Reporting Requirements	7
9. Appendix	8

1. INTRODUCTION

There is currently an incomplete understanding of disease mechanisms in Progressive Multiple Sclerosis (PMS), and a lack of validated, reliable, and specific biomarkers (clinical, imaging, other) for identifying and tracking PMS. These factors represent major obstacles in PMS research, routine monitoring, the clinical care of PMS patients, and have hindered the development of PMS treatments. The overarching objective of this proposal is to overcome these gaps and identify novel, specific correlates of disease progression in PMS. The principal hypothesis underlying this proposal is that distinct and specific retinal changes occur in PMS, namely INL and ONL atrophy.

The first aim of this study is to confirm and validate that INL and ONL retinal atrophy predominate in PMS and have specific utility for tracking PMS. The second aim of this study is to determine whether rates of GCIPL, INL and ONL atrophy are lower in ibudilast versus placebo treated PMS patients, and evaluate the relationships of OCT captured treatment effects with broad spectrum clinical and MRI measures. To achieve the objectives and specific aims, this project is utilizing pre-existing OCT and other data acquired from a well-characterized, adequately controlled, study of ibudilast in patients with PMS with sufficiently powered cohorts as part of the SPRINT-MS trial (a 96-week, randomized, double-blind, placebo controlled study of the phosphodiesterase inhibitor ibudilast in 255 primary and secondary PMS patients - 126 randomized to placebo and 129 to ibudilast treatment). Study participants underwent clinical and imaging (including OCT) assessments every 24 weeks. The study found that relative to placebo, ibudilast reduced rates of whole brain atrophy in PMS by 48% and may indeed be neuroprotective, highlighting the study cohort as opportune to meet the objectives of the current project.

2. KEYWORDS

Multiple sclerosis, progressive multiple sclerosis, optical coherence tomography, ibudilast, phosphodiesterase inhibitor, ganglion cell and inner plexiform layer, inner nuclear layer, outer nuclear layer.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Aim 1: To confirm and validate that INL and ONL retinal atrophy predominate in PMS and have specific utility for tracking PMS.

Aim 2: To determine whether rates of GCIPL, INL and ONL atrophy are lower in ibudilast versus placebo treated PMS patients, and the relationships of OCT captured treatment effects with broad spectrum clinical and MRI measures.

What was accomplished under these goals?

In order to achieve the aims of this study, high quality segmentation and quality of OCT data for both the placebo and ibudilast arms is required. Significant progress was made towards these project goals, with completion of all of the second year milestones of this three-year project:

- 1) All scans were run through segmentation (projected months 10-16)
- 2) Quality control was performed for all segmented OCT data. Scans were manually reviewed for any segmentation failures. Borderline cases were flagged and given a second review. Data segmentation data was reviewed for to identify outlying OCT data values or outlying changes using numeric and graphic methods, and these outliers were given an additional review to check for any segmentation failures (projected months: 16-21).
- 3) High quality segmentation was achieved for all placebo and ibudilast arm OCT data (projected month: 21)

- 4) The segmented OCT data were combined with the clinical and MRI data from the SPRINT trial in a single comprehensive dataset. Data were validated and data with similar dates were linked (projected months: 21-25)

All tasks planned to be performed during the first and second year of this study have been satisfactorily completed in accordance with our pre-planned statement of work. Progress is underway on the goals of the third year of the study. The next ongoing step is the statistical evaluation of GCIPL, INL, and ONL atrophy and their relationships with clinical and MRI measures. Progress has been satisfactory, with notable findings related to differential treatment-response to ibudilast by subgroup. Based on preliminary findings, additional goals for the project have been identified: query the association between markers of acute inflammation including neurofilament lightchain and new MRI lesions with subtype differences in treatment effect, continue to analyze the associations between OCT and clinical markers using standard thresholds of clinical marker progression, and expand clinical data analyses to include data from questionnaires collected during the study (including the EuroQol Questionnaire, the Suicide Behaviors Questionnaire, and the Short Form 36 Questionnaire).

What opportunities for training and professional development has the project provided?

The project has provided opportunities for post-doctoral fellows in the Saidha lab to learn several of the techniques required for this project, specifically, training on the use of the Johns Hopkins segmentation and quality control of OCT imaging as well as the management, systematic organization, and statistical analysis of clinical data.

How were the results disseminated to communities of interest?

Preliminary analyses related to GCIPL, INL, and ONL atrophy and their relationships with PMS subtype, clinical data, and MRI data have resulted in an abstract submission to the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). This submission was selected for an oral presentation, so the data will be presented at ECTRIMS via the virtual presentation platform on October 15th, 2021, and a related manuscript is currently in progress.

What do you plan to do during the next reporting period to accomplish the goals?

Over the course of the next reporting period, we will finish analyzing the OCT data and its relationships with the clinical and MRI data and evaluate the role of INL and ONL measurements as biomarkers in PMS. We will complete our analysis of the neuroprotective effects of ibudilast and explore how the differential treatment effects we found may suggest PMS and PMS-subtype specific disease processes. We will prepare and submit these results for publication.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the report?

We have measured the neuroprotective effect of ibudilast in PMS via the reduction of GCIPL atrophy, and found a different response based on PMS subtype which is similar to previously published MRI findings. These findings may help guide the selection of suitable populations for the use of ibudilast and may contribute to determining PMS and PMS-subtype specific disease processes.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6. PRODUCTS

Publications, conference papers, and presentations

- **Journal publications:** Manuscript in progress

- **Books or other non-periodical, one-time publications:** Nothing to report

- **Other publications, conference papers, and presentations:** An abstract has been submitted to the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, and it has been accepted for an oral presentation which will occur on October 15th, 2021.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Shiv Saidha PI N/A 2 Dr. Saidha oversees all facets of the project as outlined in the main body of the application.
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Jerry Prince Co-Investigator N/A 1 Maintains the optimization of the OCT segmentation software package

Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Henrik Ehrhardt Post-Doctoral Associate N/A 6 Performs quality control assessments of all imported/transferred OCT data, and quality control of the segmentation data. Performs statistical analyses and prepares materials for submission.
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Anna DuVal Project Coordinator N/A 1 Participated in the coordination of the SPRINT-MS data. Facilitated discussion to resolve technical issues. Provided logistical guidance for segmentation and quality control process.
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Agustina Quiroga Project Coordinator N/A 6 Performed segmentation and participated in the quality control process.
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Yufan He Project Coordinator N/A 6 Assisted in the maintenance of the optimization of the OCT segmentation software package; resolved technical issues.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

- **Organization Name:** Cleveland Clinic
- **Partner's contribution to the project:** Provided access to and will provide knowledge of the study-specific data necessary to perform the analyses proposed in the current proposal and interpret the results.
- **Facilities:** Nothing to report.
- **Personnel exchanges:** Nothing to report.
- **Other:** Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Collaborative awards

Nothing to report.

Quad charts

Nothing to report.

9. APPENDIX

Award chart

W81XWH-19-1-0631: Inner and Outer Nuclear Layer Atrophy of the Retina as Novel and Distinguishing Biomarkers for Defining and Tracking Progressive Multiple Sclerosis

PI: Dr. Shiv Saidha, Johns Hopkins University, Maryland

Budget: \$936,683.00

Topic Area: Multiple Sclerosis Research Program

Mechanism: W81XWH-18- MSRP-IIRA



Research Area(s): 0417, 0505, 0701, 0704, 0714, 0803, 0807, 1405, 1407 **Award Status:** Aug 15, 2020 - Aug 14, 2021 (Year 2)

Study Goals:

Use optical coherence tomography (OCT) to identify novel, specific correlates of disease progression in progressive multiple sclerosis (PMS) and examine the effects on the new phosphodiesterase inhibitor ibudilast in relation to both imaging and clinical outcomes.

Specific Aims:

Aim 1: To confirm and validate that INL (inner nuclear layer) and ONL (outer nuclear layer) retinal atrophy predominate in PMS and have specific utility for tracking PMS.

Aim 2: To determine whether rates of GCIPL (ganglion cell inner plexiform layer), INL and ONL atrophy are lower in ibudilast versus placebo treated PMS patients in the recent SPRINT-MS Trial, and to examine the relationships of OCT-captured treatment effects with a broad spectrum of clinical and MRI measures.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date

All second year milestones for this three-year project have been completed:

- 1) All scans have been run through segmentation
- 2) All scans segmentations have undergone quality control
- 3) High quality segmentation has been achieved for all placebo and ibudilast arm OCT data
- 4) OCT, clinical, and MRI data have been combined and validated

Third year milestone progress: Data analysis is proceeding in accordance with the projected timeframe