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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

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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- and second-year milestones have been successfully completed. Year three milestones are in progress and moving towards meeting the overall project objectives, to determine 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.

15. SUBJECT TERMS
Multiple sclerosis, progressive multiple sclerosis, optical coherence tomography, ibudilast, ganglion cell and inner plexiform layer, inner nuclear layer, outer nuclear layer.

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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, and 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 to 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 quantitative and qualitative quality control of OCT data for both the placebo and ibudilast arms was required. This was achieved and significant progress was made towards the project goals of organizing and analyzing data. Specifically, many third-year milestones of this project were completed:

1) Organize all OCT, clinical and MRI data from the placebo and ibudilast arms, including quality control of all data, to permit analysis (months 25-30)
2) Statistical evaluation of rates of GCIP, INL, ONL atrophy between arms (months 31-32)
3) Statistical evaluation of rates of GCIP, INL, ONL atrophy in relation to changes in MRI measures (months 33-34)

4) Statistical evaluation of rates of GCIP, INL, ONL atrophy in relation to changes in clinical measures (months 35-36)
5) Manuscript preparation for submission suggesting that GCIPL rates of atrophy are decreased in the ibudilast arm in comparison to the placebo arm, predominantly in patients with Primary PMS and not Secondary PMS (months: 30-36).

Progress on statistical evaluation of rates of retinal atrophy has been satisfactory. Thus far, notable findings related to differential treatment-response to ibudilast by subgroup identified, whereby the treatment effect appears to be mainly driven by the primary PMS and not the secondary PMS cohort. These findings are being prepared as a manuscript for submission for publication. During this project period we have begun to make progress on evaluating the association 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). In the next project period we expect to query new MRI lesions with subtype differences in treatment effect.

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, statistical analysis of clinical data, manuscript preparation and submission.

How were the results disseminated to communities of interest?
Analyses related to GCIPL, INL, and ONL atrophy and their relationships with PMS subtype, clinical data, and MRI data in both the ibudilast and placebo arms have resulted in an oral presentation of an abstract at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), which occurred on October 15th, 2021, and preparing a manuscript that is due to be submitted for review at *Neurology*. This submission will be eventually published and its content will be available to the general public.

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 complete data analysis, further manuscript preparation and submission. We will explore the associations between OCT and clinical data collected during the study (including the EuroQol Questionnaire, the Suicide Behaviors Questionnaire, and the Short Form 36 Questionnaire). We will prepare and submit these results in a second paper 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 differential treatment effect between primary and secondary PMS groups. These findings may have major implications for our understanding of PMS subtype pathobiology, mechanism of action of ibudilast, and future PMS clinical trial designs. It also further supports the utility of OCT measures as outcome measures, reflecting global CNS processes in PMS cohorts.

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 near completion for submission
- Books or other non-periodical, one-time publications: Nothing to report
- Other publications, conference papers, and presentations: An oral presentation of an abstract at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), October 15th, 2021; another abstract is being prepared for submission to the eighth annual Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2023.

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:	Jerry Prince Co-Investigator N/A 1

Contribution to Project:	Maintains the optimization of the OCT segmentation software package
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Hussein Moussa Post-Doctoral Associate N/A 4 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:	Henrik Ehrhardt Post-Doctoral Associate N/A 8 Performed quality control assessments of all imported/transferred OCT data, and quality control of the segmentation data. Performed statistical analyses and prepared materials for submission.
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Anna DuVal Project Coordinator N/A 1 Provided logistical guidance for segmentation and quality control process.

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, 2021 - Aug 14, 2022 (Year 3)

Study Goals:

Use of optical coherence tomography (OCT) to identify novel, specific correlates of disease progression in progressive multiple sclerosis (PMS) and examine the effects of 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 GCIP (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

Many third-year milestones for this project have been completed:
1) Organize and quality control data for analysis
2) Statistical analysis for the rates of retinal layer thicknesses has been performed
3) Correlations between retinal layer thicknesses and whole brain atrophy were explored
4) A manuscript illustrating the study findings is being prepared to be submitted to a peer-reviewed journal

Upcoming 1-year NCE period: Finalize initial manuscript for publication; continue data analyses for additional manuscripts.