MCLENA-1: a Phase II clinical trial for the assessment of safety, tolerability, and efficacy of lenalidomide in patients with mild cognitive impairment due to Alzheimer's disease; Trial Design and Rationale

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ABSTRACT

Accumulating evidence indicates that inflammation is prominent both in the blood and central nervous system (CNS) of Alzheimer's disease (AD) patients. These data suggest that systemic inflammation plays a crucial role in the cause and effects of AD neuropathology. Capitalizing on our experience from a previous clinical trial with thalidomide, here, we hypothesize that modulating both systemic and CNS inflammation via the pleiotropic immunomodulator lenalidomide is a putative therapeutic intervention for AD if administered at a proper time window during the course of the disease. Thus, in this Phase II proof-of mechanism study, amyloid positive, single and multiple domain amnestic mild cognitive impairment (aMCI) subjects will be treated with 10 mg/day of the immunomodulator, anti-cancer agent lenalidomide for 12 months on a 1:1 ratio (15 placebo + 15 drug-treated subjects total), followed by a 6 months washout period. The primary objective of the study is to determine the effect of 12 months of lenalidomide treatment on cognition, which is assessed via a battery of cognitive tests administered at regular intervals. The secondary objective is to assess the safety and tolerability of lenalidomide in aMCI patients evaluated through adverse events, clinical tests (hematology, serum chemistry, urinalysis), vital signs, physical and neurological examinations, and electrocardiograms. Tertiary objectives are to analyze the effects of lenalidomide on brain amyloid loads (Florbetapir PET imaging), as well as neurodegeneration (volumetric MRI), by comparing pre- and post-dosing data. Finally, exploratory objectives will investigate wether blood inflammatory markers can serve as surrogate markers of therapeutic efficacy for our study drug. Our study should allow determining whether or not lenalidomide is safe in subjects suffering neurological disorders, and whether it can alter the clinical course of AD when administered before dementia onset.

RATIONALE

There are currently no FDA-approved medications indicated for the treatment of AD. All monotherapy clinical trials with a focus on disease modification completed to date have failed to meet the clinical endpoint of significantly slowing cognitive decline in dementia due to Alzheimer's disease (AD), including BACE1 inhibitors, γ-secretase inhibitors and modulators, and active and passive immunization against monomeric, oligomeric, and protofibril amyloid beta (Aβ). Surprisingly, the failure of BACE1 inhibitors in recent clinical trials was associated with exacerbation of cognitive decline, in addition to displaying toxicities due to the inhibition not only of amyloid precursor protein processing, but also by blocking the processing of all BACE1 substrates with various affinities. This emphasizes the urgent need for novel therapeutic approaches able to reduce several AD neuropathologies simultaneously, without worsening cognition.

Inflammation is prominent in many neurological disorders, yet no clinical trial has demonstrated the efficacy of anti-inflammatory agents for AD. Critical is the fact that chronic peripheral low-grade inflammation is associated with aging and increases the risk for disease and mortality, including AD. Interestingly, the anti-cancer drug lenalidomide is one of the very few pleiotropic agents that not only lowers the expression of TNF-α, IL-6 and IL-8, but also increases the expression of anti-inflammatory cytokines (eg IL-10), thus it modulates both innate and adaptive immune responses.

Preliminary test showed a significant decrease in brain TNF-α mRNA, BACE1 mRNA and protein levels, and Aβ plaque loads, as well as improved cognitive measures in APP23 mice administered lenalidomide. Therefore, capitalizing on our experience with a recent thalidomide clinical trial we conducted in house and on our animal observations, in the current project we aim to test the central hypothesis that lenalidomide reduces inflammatory and AD-associated pathological biomarkers, and improves cognition.

STUDY DESIGN

This study was reviewed and approved by the Cleveland Clinic Institutional Review Board (IRB; protocol #19-658). The investigators will regularly report the progress of the study to a medical monitor, a data and safety monitoring board (DSMB), and the IRB for compliance and investigational drug safety purposes. The Food and Drug Administration approved the use of lenalidomide for this project under Investigational New Drug Application (IND) #142121.

Design Summary: This is an 18-month, Phase II, proof-of-mechanism, double-blind, randomized, placebo controlled clinical study where 30 patients with aMCI will be administered 10 mg/day lenalidomide for 12 months followed by a 6 month washout.

Main Inclusion Criteria: All subjects will be aMCI with brain amyloid loads (18F-florbetapir), aged 50-89, with a supervised caregiver spending at least 10h/week with the patient.

Main Exclusion Criteria: Patients living alone, or with other neurodegenerative conditions,, and with neutropenia and/or thrombocytopenia.

Consent, Assessments, and Randomization: All participants (or their legally authorized representative) and their caregiver will sign an IRB-approved inform consent form. Consent can be withdrawn at any time for any reason. Patients entering the clinical trial will undergo the assessments listed in Table 1. Subjects are randomized by our biostatistician.

Drug and Dose Selection: Lenalidomide has lasting immunomodulatory effects, improving both cellular and humoral immune functions7. Its main modes of action are via: i- the destabilization of TNFα mRNA, and inhibition of IL-1, IL-6 and IL-12 production from human peripheral blood mononuclear cells; ii- via the induction of T cell proliferation, and enhancement of IL-2 and interferon γ (IFNγ) production; iii- via the regulation of ubiquitination processes. Additional mechanisms likely take place in non-cancer cells, but have not been fully identified yet.

***Table 1*: Schedule of Visits**

	WK -6/-2	WK 0	WK 1	WK 2	WK 4	WK 6	WK 8	WK 12	WK 16	WK 20	WK 24	WK 28	WK 32	WK 36	WK 40	WK 44	WK 48	WK 52	WK 56	WK 78
	Screening	Baseline	Telephone			Telephone			Telephone		Telephone		Telephone		Telephone		Telephone	End of Treatment		Follow Up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20
Inclusion/Exclusion	X																			
Informed Consent	X																			
Medical History/ Verify Diagnosis	X																			
Height, HIV test, Hepatitis B and C Tests	X																			
Pregnancy Test (women only)	X																			
Interim History		X		X	X		X	X		X		X		X		X		X		X
EKG	X				X			X				X						X		X
Vital Signs and Weight	X	X		X	X		X	X		X		X		X		X		X		X
Neuro and Physical Exam	X	X		X	X		X	X		X		X		X		X		X		X
Amyloid imaging (if none done in past 12 months)	X																	X		
Volumetric MRI (if none done in past 12 months)		X																X		
CT Scan (if none done in past 12 months)	X																			
LP (Optional)		X																X		
Labs (CBC, CMP, UA)	X	X		X	X		X	X		X		X		X		X		X		X
Blood Biomarkers		X		X	X		X	X		X		X		X		X		X	X	X
Cognitive Assessments	X[a]	X[b]						X[c]				X[d]				X[c]		X[e]	X[f]	X[g]
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study drug		X		X	X		X	X		X		X		X		X				
Drug Accountability				X	X		X	X		X		X		X		X		X		

[a] Screening: MMSE + Hachinski + Geriatric Depression Scale
[b] Baseline: ADAS-cog + CDR-SOB + ADCS-ADL
[c] 3 and 9 months: ADAS-cog
[d] 6 months (half-way through drug treatment): ADAS-cog + CDR-SOB
[e] 12 months (end of drug treatment): ADAS-cog + CDR-SOB + ADCS-ADL
[f] 12 month + 4 weeks washout: MMSE + ADAS-cog + CDR-SOB + ADCS-ADL
[g] 18 months (6 months washout): MMSE + ADAS-cog + CDR-SOB + ADCS-ADL

Drug dosing is crucial for this clinical trial. Our previous thalidomide trial failed because of too many adverse events (AEs) related to high drug doses. Thus, with lenalidomide we want to use a dose range known to be effective (5-10 mg/day), but that induces the minimum toxicity possible in non-cancer subjects. Here, safety dictates a fixed dose rather than an escalating dose regimen.

Primary Outcome Measures: To date, the main measure for an effective AD treatment is cognition. Therefore, any inflexion of cognitive decline will be the only clinical validation of disease improvement. Here, we will use Alzheimer's Disease Assessment Scale - Cognitive (ADAS-cog), Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), Clinical Dementia Rating - Sum of Boxes (CDR-SOB), and Mini Mental State Examination (MMSE). The tests will be used in alternation to avoid that subjects memorize them simply by multiple administration, as specified in Table 1.

Secondary Outcome Measures: Our secondary outcome measures are safety and tolerability of the drug in aMCI subjects assessed via regular clinical laboratory tests, electrocardiograms, and neurological exams (Table 1). Tolerability of lenalidomide in study subjects will be derived from the frequency of adverse events (Aes) and study withdrawal motivated by subjects' discomfort during the dosing period.

Tertiary and Exploratory Outcome Measures: In an effort to identify theragnostic markers, we will explore three main measures:

1. Brain amyloid loads (18F-florbetapir imaging following the ADNI protocol) comparing mean SUVr for pre- and post-dosing from 6 .
2. Volumetric MRI imaging will be carried out pre- and post-dosing to assess hippocampal, ventricular, and whole brain volumes, as well as cortical thickness.
3. We will explore the possibility of using blood inflammatory markers (e.g. C-reactive protein, TNF-α, IL-1β, IL-6, IL-8, and IL-10) as surrogate markers of lenalidomide efficacy.

DISCUSSION

Alzheimer's disease is a multifactorial and complex neurodegenerative disorder with multiple symptoms and pathophysiological processes developing over time27. Consequently, the use of monotherapies with very precise targets is unlikely to slow down or cure the disease. Instead, the use of combination or pleiotropic therapies will likely be more successful to treat the disease28. Furthermore, because scientists are currently unable to regenerate brain tissue with encoding of personal memories, the first successful AD therapies will likely be administered at early stages of the disease, i.e. before severe neurodegeneration develops. In the present clinical trial, we will use the pleiotropic immunomodulator lenalidomide on amyloid positive aMCI subjects to assess its potential at slowing down the clinical progression of AD over a year of treatment. Because nothing is known about the study drug in the context of neurological disorders, our first study is a proof of concept trial conducted on a small number of subjects to determine whether lenalidomide could be used as an AD prevention therapy in the future. To reach this goal, we have carefully selected clinically relevant endpoints, including cognitive measures, amyloid brain imaging, and volumetric MRI. Further, we will explore the theragnostic potential of minimally invasive and affordable blood biomarkers to assess treatment efficacy, and we will compare those peripheral markers to clinical markers (i.e. cognitive measures, amyloid imaging, and volumetric MRI). Given the urgent need for therapeutic interventions to prevent the AD pandemic predicted to happen in the coming decades29, we strongly believe that repurposing clinically relevant drugs in well-defined pilot studies will dramatically accelerate the discovery of the first effective AD treatments, that will, then, provide ground to develop novel interventions while minimizing toxicity. The present study is entirely designed to obtain accurate data about the repurposing of lenalidomide for AD treatment in the shortest time possible.

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