Maraviroc to Augment Rehabilitation Outcomes After Stroke (MAROS)

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Maraviroc To Augment Rehabilitation Outcomes After Stroke (MAROS) Protocol
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Background

After stroke, the combination of progressive skills practice in an adequate dose, exercise for fitness, and reduced sedentary time will augment motor and cognitive outcomes. Sensorimotor and cognitive improvements after stroke often reach a general plateau by approximately 12 weeks after onset, however. Drugs that might enhance learning or neural repair, as well as other molecular and synaptic adaptations that occur during skills training and fitness exercise, might extend that recovery curve, although to date only fluoxetine has given any hint of this. Most trials have tested agents that modulate neurotransmitters. Several very recent preclinical experiments and observational studies in patients after stroke suggest that the commercially available medication, Maraviroc, may augment skills learning during rehabilitation training especially during the first three months after onset, by acting on unique molecular components for novel learning.

The C-C chemokine receptor 5 (CCR5) is a seven-transmembrane G protein-coupled receptor that mediates HIV virus cellular entry. Individuals who are homozygous for a 32 base pair deletion in the CCR5 gene (CCR5D32), and subsequently do not express functional CCR5, are highly protected from infection with R5 HIV-1. The receptor is expressed in microglia, astrocytes and neurons in many regions of the brain. Dr. Alcino Silva at UCLA postulates that this receptor is involved in learning and memory. In a series of elegant experiments, he showed 1) CCR5 deficiency results in enhancements in hippocampal learning and memory and in experience-dependent sensory plasticity; and 2) CCR5 overexpression leads to learning and memory deficits. Decreasing the function of CCR5 increases MAPK/CREB signaling, long-term potentiation, hippocampus-dependent memory, and neocortical experience-dependent plasticity. Ligand binding to CCR5 is known to modulate several parallel signaling cascades implicated in learning and memory, including the suppression of adenyl cyclase, as well as the activation of the PI3K/AKT and P44/42 MAPK signaling. These findings support the application of brain permeable CCR5 antagonists, not only as a combination drug in antiretroviral therapy, but also as a treatment for cognitive deficits caused by HIV. In addition, the studies suggest that the receptor is a novel target to augment learning and memory in those with cognitive and motor deficits in relation to training.

Several preclinical models of stroke and traumatic brain injury from Drs. ST Carmichael, Alcino Silva, and Esty Shohami suggest that the FDA-approved CCR5 reversible co-receptor antagonist, Maraviroc, may lead to better motor outcomes when combined with training, presumably due to enhanced learning. Stroke induces CCR5 expression in neurons in the first month after onset in a mouse model (Carmichael). Knockdown of CCR5 in the motor cortex of adult mice improves recovery after stroke (Carmichael and Silva et al). Maraviroc also improves motor recovery in this model. An Israeli post stroke observational trial (TABASCO, Einor Ben Assayag, et al.) enabled a test of the effects of a naturally occurring loss of function mutation in CCR5 (CCR5 delta32). About 15% of the Ashkenazi Jewish population carries the deletion (CCR5 rs333 - Δ32). This group in TABASCO had better outcomes for walking speed and the Berg Balance Scale. A Washington University observational study that included some subjects with this deletion also looked positive for better outcomes, but was more equivocal, based on differences in stroke type. Neither gene association study has been published yet.

Maraviroc is the only CCR5 antagonist currently approved by the United States Food and Drug Administration, the European Commission, Health Canada. Maraviroc (Selzentry, Pfizer) is a small molecule currently approved for treatment of patients infected with R5-tropic HIV-1. It is metabolized by CYP3A4. The dose may have to be adjusted when given with CYP3A4 inducers or inhibitors, primarily drugs that are also used for HIV therapy, but also for

several anticonvulsants. None of the subjects in the proposed trial will be entered if on these medications. The drug has a good pharmacokinetic profile with relatively low protein binding and high bioavailability when given at standard doses twice a day. It is moderately lipophilic, so it can penetrate the blood-brain barrier. At a single dose of 300 mg, time to maximum concentration occurred by two hours post-treatment in humans. The terminal half-life is 14-18 hours, so a single dose used during the time of training in the proposed protocol should be adequate, rather than the BID treatment for AIDS. Despite low CSF concentrations, the drug suppresses CSF viral load. It potently inhibits downstream CCR5 signaling and does not induce CCR5 internalization, suggesting that the drug is a functional CCR5 antagonist.

Aims

Given the potential for Maraviroc to augment rehabilitation training, we will carry out a trial of Maraviroc in patients with disabilities severe enough to have required inpatient stroke rehabilitation and, based on our preclinical data, who can start the drug intervention within 6 weeks of stroke onset. We plan a parallel group, randomized controlled pilot trial at three sites, UCLA SOM, Yale University SOM in New Haven, and Burke Neurological Research Institute in White Plains, NY, to gather enough entries in a shorter time and to better generalize the results of this phase II/III pilot trial. We will compare usual post-stroke care plus placebo versus Maraviroc given for 8 weeks in 60 participants (up to 66 to account for dropouts). The primary outcome measurements will be gains in walking and functional use of the affected upper extremity, continuously monitored remotely, as well as formally assessed at 4 and 8 weeks after initiating the drug and at 6 months (primary endpoint) post stroke onset. To try to maximize the amount of practice that is most relevant to the primary outcome measurements and determine whether or not Maraviroc can enhance the effects of training, as hypothesized, all participants will be monitored by mobile health devices we developed and will receive weekly encouragement, based on device data, to walk, reduce sedentary time, and reach and grasp in the home in between usual care therapies. The amount of use of these telerehabilitation devices will be a nested substudy of feasibility.

We will look for a behavioral marker of the potential effect of Maraviroc by testing each subject while on and off the assigned medication with several commonly used neuropsychological tests of motor and hippocampal learning.

The trial will be registered at ClinicalTrials.gov with ethical approval from the UCLA medical IRB.

Hypothesis 1: Subjects who take Maraviroc plus outpatient and home-based rehabilitation therapy managed remotely will improve significantly more in the primary outcomes of walking speed and upper extremity function by the Action Research Arm Test (ARAT) compared to the placebo drug group at the 6-month post stroke assessment.
Hypothesis 2: The feasibility of home-based telerehabilitation practice will be revealed by the finding that at least 75% of all participants will have achieved compliance for at least 150 minutes of walking and 100 minutes of reach and grasp practice weekly.

Methods

Consent Process:

Participants will be identified from the inpatient stroke rehabilitation admissions to the UCLA affiliated California Rehabilitation Institute (CRI) and from referrals to the Burke Neurological Research Institute in NY and to the Stroke Service in the Department of Neurology

at the Yale University SOM. The Burke and Yale sites will have their own IRB reviews managed by the PIs.

Patients at CRI must check a box that is in the content of their admission papers to be willing to be contacted about research. The CRI Research Committee will let investigators know about those patients who opt in to be contacted and carry the diagnosis of stroke. After a brief chart review of this group, potentially eligible participants who are still at CRI or were discharged in less than 2 months since onset of stroke will be contacted by Drs. Michael Su or Bruce Dobkin to hear about the aims of the trial and gauge interest, preferably with a significant other present. If the potential subject wishes to learn more, one of these physicians will discuss the trial in detail and begin the process of Informed Consent. Potential participants who are still CRI inpatients may wish to defer a decision until the time of discharge or within the first two weeks after discharge from CRI. We do not plan any interaction with potential participants other than in their private room at CRI or in an outpatient neurology clinic room at UCLA.

In addition, a flyer (submitted) will be posted in the lobby and on the stroke unit at the California Rehabilitation Institute (CRI). The flyer will also be given to physicians to hand to their possibly eligible patients.

Eligibility:

Inclusion criteria include transfer to inpatient rehabilitation within 4 weeks of stroke onset; single ischemic or subcortical hemorrhagic infarct; age >30 years and <86; at the time of randomization, hemiparesis with 4/5 or less strength at the shoulder flexors and at least 3 finger extensors, and the hip and ankle flexors and extensors, as well as a Functional Independence Measure (FIM) score for ambulation ≥3 to walk at least 10 steps; caregiver available for at least two hours a day for practice and transportation when needed; adequate language skills to read and understand the Informed Consent and retain information during daily therapies.

Exclusion criteria include prior stroke with persisting motor impairment or disability; limited resources or illness that will not enable a return to living outside of a facility; any medical condition that had limited daily physical activity to walking no more than 2 blocks outdoors prior to the stroke (e.g., claudication, congestive heart failure or lower extremity pain); history of dementia or MMSE score <24; history of hepatitis or elevated hepatic transaminases or bilirubin; history of renal insufficiency or serum creatinine over 1.6; and cancer or other chronic illness that makes 3-year survival unlikely or will detract from the ability to carry out exercise and skills practice.

Randomization:.

Participants will be assigned to the control or experimental group using a 1:1 computer-generated randomized allocation schedule in the REDCap clinical database. Assignment (for both research sites) occurs automatically upon the entry of eligibility criteria.

All members of the research team and the subjects will be blinded as to allocation. The study statistician and the rest of the Safety Committee will have access to the assignment if necessary (e.g., adverse drug reaction).

Each site will enter 20-25 subjects, approximately half into each of the trial arms. Entries will be accomplished within 30 months with follow-up assessments and data analyses by the end of 36 months.

Baseline Studies:

We will collect age, gender, body mass index, ethnicity, living place, work status, caregiver support, date of stroke, date of transfer for inpatient rehabilitation, lesion type (TOAST) and location, personal risk factors for stroke, medications, and FIM for level of pre-stroke walking and ADLs. We will measure the National Institutes of Health Stroke Scale (NIHSS), British Medical Council manual muscle exam for eligibility, motor FIM score, 10-m

walking speed, 6-min walking distance, a video-recorded assessment of upper extremity kinematics that does not show the subject's face, and Action Research Arm Test (ARAT). We will record the average two blood pressures and heart rates on the day of entry and the most recent HbgA1c and lipid panel, liver function tests, creatinine/BUN, and MRI/CT imaging results from the inpatient rehabilitation medical record. If liver function tests or creatinine cannot be found, the tests will be obtained at the outpatient research site as a cost to the study. Dr. Dobkin will review each imaging study to localize the relevant stroke lesion by consensus. An email address and phone number for the patient and a close contact will be kept separate from the clinical database by the coordinator.

Interventions:

Maraviroc: Medications are often in flux during inpatient rehabilitation, so Maraviroc or placebo will be started within two weeks of discharge, which most often will occur from 4-6 weeks after stroke onset. A 1-month supply of capsules will be handed to participants after the Consent has been signed, baseline measurements obtained, and randomization assigned, usually on the same day. The second 1-mo supply will be provided during a scheduled interim measurement assessment at UCLA near the end of the 4th week on medication. Pill counts will be taken on the returned bottle. Participants will take either *Maraviroc or a placebo at a dose of 300 mg at 6-8AM.* The capsules will be supplied by the UCLA, Burke and Yale pharmacies to each respective site and used under an IND and IRB protocol as required by each institution.

Based upon Pfizer's reports on premarketing and post marketing studies of Maraviroc and our review of the literature, no dose adjustment is necessary in patients with even mild-to-moderate renal impairment. The drug does not affect the QT interval. At high doses (600mg or more), it may induce orthostatic hypotension, so it is recommended that *users who also take an anti-hypertensive medication be asked about symptoms of orthostatic hypotension*. Of note, 8% of patients in active and placebo drug groups described orthostatic symptoms in a large trial. In HIV trials, 1.3% of subjects had cardiovascular events, more than in the placebo group, but the link to the drug was unclear and symptoms occurred only in those with known cardiac disease. Also, no greater incidence of infection, rash or other CNS symptoms was noted in these subjects. An occasional Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms did occur (seen only in post marketing surveillance, not in controlled trials), so *complaints of rash, fever, joint or muscle aches, blisters, facial edema, etc. will be part of our weekly phone call surveillance plan*. Participants will be told to stop their medication immediately should such symptoms occur and their physician notified. Of note, St John's wort should not be used with the medication since it decreases the concentration of Maraviroc

The drug is metabolized by the liver, so using it in persons with more than mild hepatic disease, especially in the presence of a CYP3A inhibitor, would have to be closely monitored; our participants will be free of hepatic, as well as renal impairment. The recommendation from the FDA is to obtain liver function tests prior to starting the drug and again should symptoms such as rash or hepatitis occur. This rather rare adverse reaction tends to occur at about one month after starting the medication (in less than 4% on the drug or placebo) , *so we will obtain a bilirubin and transaminases at the planned 1-month follow up*..

Adverse events related to the medication assignment, to rehabilitation practice or to other causes will be adjudicated by the Safety Committee with input from the PI.

Rehabilitation therapy: All participants will have routine outpatient or home health physical and occupational therapy after inpatient discharge as prescribed by their physicians. Each group will be contacted weekly by phone by UCLA staff only to help maintain interest in the trial, count the number of usual care physical and occupational therapy completed, assure use of the assigned medication, ask about possible adverse reactions, and to encourage them to be active. The UCLA coordinator will obtain this information and provide the feedback using a

standard script and checklist.

A unique aspect of this trial is a telerehabilitation component that aims to give feedback to all participants to practice with the affected arm and walk daily. All participants will be asked to wear an ankle sensor (Fitbit) that downloads to a computer we supply to each subject. We record lower extremity activity, including walking and cycling. Data includes daily sedentary and active time, walking speed and distance. The walking data is sent to a HIPAA compliant cloud server provided by a commercial company, FitaBase. The coordinator at each site will show each study subject and caregiver how to put on and charge the sensors. At the weekly call, participants will be reminded to try to build up to walking at least 3 times a day for at least 10 minutes per bout and reduce sedentary time. Behavioral modification techniques that we have been using successfully, based on sensor data, will be employed. All such feedback will be provided by the UCLA study group.

Participants will also be given a LEAP Motion Controller device that sits in the bottom of a 12x18” box covered by a plastic lid. This simple system enables us to monitor practice of reaching and grasping with the affected upper extremity in the home. At the weekly call from a UCLA study staff person, they will be encouraged to perform 20 minutes daily of reach, grasp and pinch actions with small common items and practice bringing the affected hand to the mouth. Items will be moved from one corner of the rectangular top to another in a fixed sequence. A unique feature of this trial is that we will have ground truth about how much they did practice, which may enable a dose-response and responder-nonresponder analysis. For example, if a subject is taking the active medication, but never practices, outcomes may be less positive than for the person who does practice as prescribed.

A data manager at UCLA will review all incoming data from the 3 sites for completeness and quality, as well as ensure proper use of the systems (e.g. make sure devices are charged regularly, automatic data uploads occur without problems, and practice data are processed correctly). The study staff at each site will assist the UCLA staff to help solve technical problems with the equipment and interact with subjects around difficulties in patient participation. At the weekly call by UCLA staff, participants will be queried from a script about any possible medical complications. Such potential adverse events will be immediately reported to Dr. Dobkin who will contact his participants or contact the local PI at Burke or Yale to interview their subjects and then report back to Dr. Dobkin.

Outcome Measurements:

The primary outcomes will be a timed walking speed over 10 meters by the blinded physical therapist and the ARAT for UE function performed by the blinded therapist. These will be obtained at baseline, then after 4 weeks on assigned medication, within 5 days of the last medication dose (8 weeks) and again at 6 months post stroke onset.

Secondary outcomes obtained at the end of drug treatment and at 6 months after stroke onset by the blinded observer will include the Fugl-Meyer Motor Assessment score for both lower and upper extremities, clinic-based 3-min walking distance, and the Stroke Impact Scale score related to quality of life. We will also assess for satisfaction and self-efficacy for practice and exercise (see Table). Exploratory studies will examine dose of practice based on LEAP data (duration, number of repetitions of reach and grasp of objects) and for walking (total daily walking practice time, sedentary time, and walking bouts of more than 5 minutes), and self-ratings about self-efficacy for exercise.

Statistical Analyses:

A recent observational trial (Lohse and Lang, 2016) found that walking speed increases at 0.1m/s per month and the ARAT increases by 2.9 points monthly within the time frame as this trial.

For the walking speed outcome, the evaluable sample size of 30 in each group will have 80% power to detect a difference in means of -0.206 (m/s), the difference between an assumed usual care walking speed of 0.51 (SD=0.28) and an assumed intervention group mean walking speed of 0.716. This assumes that the common standard deviation in the two groups and a two group t-test with a 0.05 two-sided significance level. The estimates for the mean and standard deviation for walking speed come from the LEAPS RCT (Duncan, N Engl J Med, 2011). We plan to enroll 66 patients to account for an expected 10% drop-out rate. The t-test used for the power calculation is a simplification of the mixed effects analysis plan for the primary endpoints.

For the ARAT sum score, analysis is based on a statistical power of 80% with an alpha of 5% for detecting a meaningful difference of 6 points, i.e., a 10% change, which has been suggested by several completed trials. In a stroke trial, the standard deviation was 8 points measured at 2 weeks post stroke. Again, a sample size of 60 plus 10% dropout rate should suffice.

Primary Analyses: As appropriate, t-tests, Wilcoxon rank sum, or chi-square tests will be employed to evaluate differences in baseline clinical characteristics between trial participants. Using the mixed effects model for *Hypothesis 1* should provide greater power than the t-test as it will account for the repeated observations of the endpoints over time. For *Hypothesis 2*, we will look at one aspect of the feasibility of home-based practice as the ratio of those who achieve at least 150 minutes of weekly walking (composed of bouts that exceed 5 minutes) and 100 minutes of weekly upper extremity practice using the LEAP with the whole group as the denominator. We anticipate that >75% will achieve this by the end of the intervention, based upon our preliminary studies using these devices in a chronic hemiparetic stroke population.

Secondary Analyses: Secondary outcomes listed in the Table will be evaluated using t-tests, Wilcoxon rank sum tests, or chi-square tests as appropriate. One planned secondary analysis will compare outcomes based on on whether or not participants can extend their wrist and at least 3 fingers at least 5 degrees at time of randomization, to assess for possible differences in drug responses between those with higher compared to lower levels of initial motor control. Another will compare outcomes in those who achieve the practice goals of Hypothesis 2 to those who do not in relation to drug assignment. We will not likely have enough subjects to do more than look for interesting potential future hypotheses.

Safety Committee:

A Safety Committee will serve both research sites. It will include the study statistician, a physician and an allied health clinician with training in stroke rehabilitation. It will meet before the start of the trial, every 6 months, after the first 10 subjects have completed the 2-month drug intervention, and as needed (e.g., serious adverse reaction).

Confidentiality:

All data will be entered from the study sites at UCLA, Yale and Burke into the RedCap database that will be monitored at UCLA by the study statistician for completeness. All materials related to the trial for UCLA entries will be stored in a locked cabinet in a locked room by the coordinator.

References

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Table. Measurement tools and testing schedule

Category	Test	Schedule			
		Entry	Weekly f/u for 2 mo	During treatment: at end of 4 and 8 weeks	6 mo outcomes
Study Procedures					
Screening	X	X			
Inclusion/Exclusion	X	X			
Informed Consent	X	X			
AE Assessment	X		X		
Demographics	NIH standard	X			
Disability	FIM	X			X
Mobility	10-m walk speed	X		X	X
Upper extremity fx	ARAT	X		X	X
Overall Impairment	NIHSS	X			X
Motor Impairment	Fugl-Meyer motor score	X		End of tx	X
Exercise capacity	6-min walk distance; change in heart rate	X		X	X
Lesion location and subtype	UCLA stroke anatomy form	X			
Walking activity sensors	Duration, distance, speed for bouts; sedentary time	X	X		
Upper extremity practice from sensors	Repetitions, sets	X	X		
Self-reported activity levels pre-stroke	IPAQ	X			
Self-reported activity levels post-entry	IPAQ			X	X
Depression	CES-D	X		End of tx	X
HRQOL	Stroke Impact Scale v3.0	X		End of tx	X
Sensor usage survey	Likert scale			End of tx	
Cognition	MOCA	X			X
Exercise expectations	MOEES	X			X
Social support for activity	Likert scale	X		End of tx	X
Exercise enjoyment	PACES	X		End of tx	X
Self-efficacy for activity	ESFS	X		End of tx	X

To include record of reasons for non-participation.
Adverse events=AE; Center for Epidemiological Studies Depression Scale = CES-D; Exercise Self-Efficacy Scale=ESFS; Functional Independence Measure=FIM; International Physical Activity Questionnaire short form=IPAQ; metabolic equivalent minutes per week=METm/wk; Multidimensional outcome expectations for exercise scale=MOEES; Physical Activity Enjoyment Scale=PACES