Use of Imaging in Restorative Stroke Trials

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***Abstract*—**Restorative therapies aim to improve behavioral outcome after stroke by promoting repair and restoration. Measures of CNS injury and function might be useful to evaluate such therapies in a clinical trial, for example, by optimizing patient selection or treatment dose. These issues are considered in this review, with specific examples provided. **(*Stroke*. 2009;40[suppl 1]:S28-S29.)**

Key Words: stroke ■ plasticity ■ recovery ■ brain mapping

A restorative stroke trial is one that evaluates a restorative therapy in patients with stroke. A restorative therapy can be defined as one that aims to improve outcome by promoting repair and restoration rather than by salvaging acutely threatened tissue. If stroke is considered to be expressed in three phases (Figure), a restorative trial would take place in the subacute or chronic phase.

Restorative interventions under study have included growth factors, cells, small molecules, intensive and activity-based therapy, robotics, neuroprosthetics, electromagnetic brain stimulation, and cognitive strategies such as motor imagery. Therapies initiated in the first few days after stroke typically remain in the preclinical[1,2] or early clinical (eg, ClinicalTrials.gov Identifier: NCT00362414) stage. Some therapies initiated in the chronic phase have demonstrated positive effects in human subjects.[3,4]

Note that the effectiveness of such interventions is influenced by activity, experience, environment, and psychosocial factors.

Imaging Measures of Potential Interest to Restorative Stroke Trials

A restorative stroke trial might incorporate any of several neuroimaging measures. In general, the purpose of using such measures is to provide insights not available at the bedside, such as those related to injury or CNS function.

A wide range of imaging measures is of potential interest toward these goals. Measures of injury include traditional anatomic methods, such as infarct volume on CT or MRI. High resolution MRI can detect changes in cortical thickness, sometimes increased with treatment. Physiological measures such as motor system transcranial magnetic stimulation (TMS) can yield information on the size of a cortical representational map, or on the speed/magnitude of the motor evoked potential (MEP), reflections of CNS injury. Diffusion tensor imaging (DTI) measures the tendency of water movement to be directional, and so reflects injury when stroke reduces the linearity of water movement within a directional tract such as the corticospinal.

Measures of tissue function might also be useful for assisting decision making in the setting of a restorative trial. Brain function can be measured with functional MRI (fMRI) or positron emission tomography (PET), as well as with electroencephalography or magnetoencephalography. Use of such methods, particularly fMRI or PET, can measure the volume of regional activation, such as the volume of Broca's area activated during a speech output task; the magnitude of activation, such as the height of parietal activation during a spatial attention task; or the balance of activation across hemispheres, sometimes reported as the laterality index. PET can provide a direct measure of regional blood flow or metabolism. Other tissue function measures include measures of excitability or inhibition, or assessments of the connectivity between various cortical regions.

Measurement of tissue function introduces complexities that do not arise with measurement of tissue structure. To activate the brain with fMRI or PET, the subject must engage in a specific behavioral paradigm, correctly, according to instructions, on cue, at times a challenge after stroke. The behavioral paradigm must be carefully selected to probe the brain functional circuit of interest.

Use of Imaging Measures in Restorative Stroke Trials

Many potential routes exist whereby the information introduced by imaging measurements might be used to improve a restorative stroke trial.

Imaging measures might be used to identify distinct patient subgroups. Selectively enriching the study enrollee pool in effect means that imaging measures might thus serve as entry criteria. For example, one might enroll only those patients with a certain amount of motor system dysfunction on the basis of the MEP measured with TMS, or on the basis of injury extent to a specific CNS functional system.

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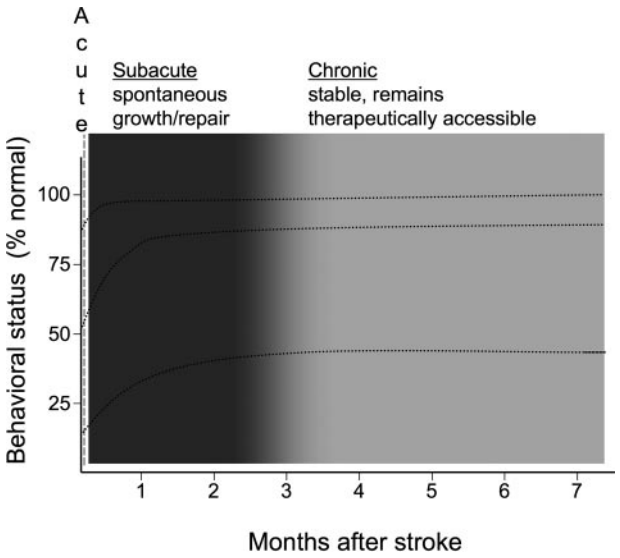

Figure. The time course of behavioral recovery is displayed for three idealized patients. Stroke can be considered as having three main phases. The acute phase is measured in hours, with treatment approaches focused on salvaging threatened tissue. A subacute phase measured in weeks follows, during which spontaneous growth-related changes might define restorative therapy targets. These changes subsequently decline in the chronic phase, which lasts an average of 8 years, as behavioral recovery is on a plateau. The success of chronic phase restorative interventions, ranging from activity-based to pharmacological, suggests some restorative targets remain for years poststroke.

Imaging measures might be used to predict treatment gains. Predictive measures might be valuable as an additional approach to refine entry criteria. Recent studies provide examples whereby a specific measure of CNS function was able to predict response to a restorative treatment; for example, a DTI-based measure of CNS injury at baseline accounted for 38% of the variance in clinical gains[5]; an fMRI-based measure of CNS function, 20%.[6] Use of such measures as entry criteria might therefore improve the ability of a clinical trial to detect a treatment-related effect. Further studies are needed to verify, and to clarify, such observations.

Imaging measures might be used to guide treatment decisions for subjects in a trial. For example, serial imaging measures can be used to individualize details of therapy, much as acute stroke trials such as the Interventional Management of Stroke II trial sometimes vary features of treatment; in that trial, choice of catheter and dose of thrombolytic were adjusted based on serial angiograms.[7] The promise of this approach in the restorative stroke trial setting was suggested by recent TMS[8] and fMRI[9] studies. Possibly, one day, such imaging measures might be used to define treatment dose and duration at the level of the individual patient.

Imaging measures might also serve as a marker of treatment effect. Such data might provide insight into treatment mechanism, which might secondarily guide features of restorative trial design. For example, fMRI studies have described changes in laterality[10] or size of motor system activation[11] in relation to a motor-based therapy. Such results might guide entry criteria (don't enroll patients with massive motor system injury), and might ultimately prove heuristic in the refinement of many aspects of restorative stroke trial design.

Summary

A large number of restorative therapies are under study. Measures of CNS injury and function can be used in many different ways to assist clinical trials of these therapies. Imaging measures hold promise to improve the ability of restorative therapies to reduce disability after stroke.

Disclosures

None.

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