Antibodies targeting this protein have been investigated in animal models of stroke and spinal cord injury with encouraging results. However, no consensus exists on the timing of drug administration after injury and its use in combination with rehabilitative physical therapy.

In a recent research article published in *Science*, Wahl and colleagues[1] investigated whether the timing of anti–Nogo-A treatment and physical therapy influenced motor recovery in a rat model of stroke. Greater than 90% of the sensorimotor cortex was destroyed using blood vessel blockade with microthrombi after training animals on a single-pellet grasping task (baseline), resulting in significant loss of fine motor skills of the contralateral forelimb. The investigators then tested 4 different combinations of drug and physical therapy schedules (Figure). In the group receiving anti–Nogo-A treatment for 2 weeks followed by a sequential skilled physical therapy regiment (anti–Nogo-A/sequential), recovery of forelimb function reached almost 90% of pre-stroke function, significantly outperforming schedules with concurrent drug treatment and physical therapy or control drugs, which only reached levels close to 40%.

To better understand why sequential administration of drug followed by physical therapy outperformed concurrent administration, the investigators performed histological analyses of cervical spine cross sections and measured corticospinal tract fibers that crossed the midline to innervate the hemicord opposite the stroke. The anti–Nogo-A/sequential treatment group had the highest number of midline-crossing fibers. In addition, using computer vision algorithms, the investigators were able to characterize this group as having a more organized radial pattern with fewer branches and a preference for the premotor/motor spinal cord rather than the sensory cord. In contrast, the anti–Nogo-A/parallel treatment group had double the number of branches, a higher bouton density, and an aberrant growth pattern preferring a different laminar distribution.

The investigators performed a final pair of experiments using short-term and long-term reversible nerve blockade to convincingly show that neurons from the intact motor cortex were the ones responsible for regeneration of the midline-crossing fibers in the anti–Nogo-A/sequential treatment group. This was done by delivering a highly efficient lentivirus containing a doxycycline-inducible tetanus toxin to the stroke-denervated hemicord at C5-6. In addition, another virus carrying a reverse tetracycline transactivator was injected into the intact motor cortex; thus, only neurons infected with both viruses were susceptible to doxycycline-inducible neuronal blockade. Indeed, after exposure to doxycycline, animals in the anti–Nogo-A/sequential group lost their new forelimb function and regained it after doxycycline cessation. A comparable design of infecting the stroke-denervated hemicord and ipsilateral intact motor cortex was taken using different viruses, and genetic elements activated by a designer drug showed similar short-term effects, confirming the location of the neurons responsible for the corticospinal tract regeneration.

Taken together, these results help describe a critical period in stroke recovery in which animals are sensitive to plasticity-inducing drugs such as anti–Nogo-A and better define how physical therapy after a period of drug exposure may contribute to optimal functional recovery. The absence of a correlation between stroke lesion size and the ability to regain function after injury is particularly encouraging for patients with large territory injuries. As providers of care for patients afflicted with motor paralysis after stroke or spinal cord injury, understanding the interplay between physical therapy timing and administration of these drugs will be critical as we design clinical trials to capture the potential of these therapies.

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A Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke Caused by Proximal Arterial Occlusion in the Anterior Circulation

Significant time and expenditure have been devoted to therapies for acute ischemic stroke, a worldwide leading cause of morbidity and mortality.[1,2] Currently, there are limited therapies approved for ischemic stroke, including care at a stroke center, initiation of aspirin, and revascularization with recombinant tissue-type plasminogen activator.

Tissue-type plasminogen activator use has a number of drawbacks, including a narrow time window, contraindications because of the risk of bleeding, and limited efficacy in recanalization of proximal major cerebral arteries.[3,4] Approximately one-third of anterior-circulation strokes are attributed to proximal major intracranial vessels, and these patients have a dismal prognosis when recanalization is not achieved.[5,6] Thus, therapies are limited in a significant number of patients with acute stroke.

Endovascular therapies have also been approved in the treatment of acute ischemic stroke, but the optimal patient selection has been unclear.[7] In the Prolyse in Acute Cerebral Thromboembolism II randomized clinical trials, patients with acute stroke had significantly better recanalization rates and outcomes when treated within 6 hours with intra-arterial prourokinase vs intravenous heparin.[8] Recently, 3 randomized clinical trials failed to demonstrate a benefit of endovascular therapy for acute ischemic stroke but helped solidify the use of recombinant tissue-type plasminogen activator in the treatment of these patients.[9-11] These trials were limited in that patients were not required to have vascular imaging to demonstrate a large vessel occlusion as the source of the stroke; thus, a number of patients were assigned to endovascular therapy that would not be beneficial. Subgroup analysis has demonstrated that analysis of only patients with large vessel occlusions revealed that patients treated with endovascular therapies had improved functional outcomes.[12]

Further limitations of these trials included the extensive number of years that it took for completion and the small number of potential patients who were included. Thus, patients receiving endovascular therapy were treated predominantly with first-generation stent retrievers. Newer generations of endovascular clot retrievers have demonstrated significantly higher recanalization rates and improved efficacy.[13,14]

To address these limitations, a number of further randomized trials were initiated. Most recently, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) was published.[15] Patients were randomized to either intra-arterial endovascular treatment (intra-arterial thrombolysis, mechanical treatment, or both) plus usual care or usual care alone (intravenous alteplase when possible). Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation confirmed on vessel imaging and that could be treated intra-arterially within 6 hours of symptom onset. The primary outcome was functional

outcome as defined by the modified Rankin Scale score at 90 days.

Patients enrolled at 16 medical centers were assigned to intra-arterial treatment (n = 233) and usual care alone (n = 267). The unequal number of patients in the 2 cohorts was due to block randomization according to preset parameters (medical center, use of intravenous alteplase, planned treatment method, and stroke severity). The mean age was 65 years (range, 23-96 years), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intra-arterial treatment. The mean time to initiation of alteplase and endovascular therapy was approximately 1.5 and 4.5 hours, respectively. There was a significantly higher incidence of functionally independent patients treated with intra-arterial therapies (32.6%) compared with the conventional therapy alone (19.1%). When significant predefined predictors of outcome were controlled for, patients receiving endovascular therapy were 1.67 times more likely to have a favorable functional outcome. All clinical and imaging secondary outcomes favored the interventional cohort. There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.

In this study, an absence of residual occlusion at the target site was more common in the intervention group (75.4%) than in the control group (32.9%). Surprisingly, good reperfusion (Thrombolysis in Cerebral Infarction score 2b or 3) was achieved in only 115 of 196 patients (58.7%) in the endovascular cohort. Prior randomized trials have demonstrated considerably higher recanalization rates with next-generation devices,[13,14] but this may be attributable to differences in patient and disease characteristics, including extent of vessel occlusions.

One of the most impressive aspects of the MR CLEAN study was that it took approximately 3 years to enroll 500 patients in a country with a population of only 16.8 million. This is likely attributable to the fact that thrombectomy devices were reimbursed by the Dutch government only when used in randomized trials. Prior international trials that included centers from larger countries took considerably longer, in part because of difficulties with recruitment. Thus, a number of studies needed to be redesigned or used obsolete technology by the time of completion. Since this publication, 3 other major stroke trials seeking to assess the role of thrombectomy in large vessel occlusion have been halted. The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) and Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) trials have been stopped because of positive interim results in favor of the intervention cohorts and results of the MR CLEAN trial. As a result of reports of these 3 trials, the Data Safety Monitoring Committee of Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial has also called for a suspension of enrollment and an early interim analysis.

These impressive trials require expedited transfer of stroke centers capable of initiating recombinant tissue-type plasminogen activator and endovascular therapies. Previous studies have demonstrated that delay in therapies, including endovascular therapies, leads to worse overall outcomes.[10,16,17] In the MR CLEAN study, general anesthesia was used in only 37.8% of patients. This may lead to the initiation of faster stroke therapies with fewer complications. The hope is that a randomized clinical trial currently underway will help define the role and necessity of general anesthesia in patients with acute ischemic stroke undergoing endovascular intervention.

In the MR CLEAN study, retrievable stents were used in 190 patients (81.5%), and other devices were used in 5 patients (2.1%). Endovascular technologies often outpace relevant clinical trials. Further studies are indicated to determine optimal endovascular strategies. Newer, more flexible catheters now allow improved clot aspiration. Aspiration with newer catheters as first-line therapy with the use of a stent retriever in patients in whom the clot cannot be aspirated has led to recanalization rates (Thrombolysis in Cerebral Infarction score 2b or 3) of up to 95% at a mean interval of 37 minutes from groin puncture.[18] Further studies are indicated to define the optimal endovascular strategies for these patients.

The authors of MR CLEAN should be applauded for their efforts. This study clearly demonstrated that endovascular therapy within 6 hours of onset of acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation is both safe and effective. This study adds to a recent meta-analysis of 6 randomized trials that found that endovascular therapy resulted in improved clinical outcomes. These results persisted even in the absence of large vessel occlusion.[19] These trials are a step in the right direction, but further studies are needed to improve potential medical therapies, critical care, imaging technologies, endovascular interventions, and patient selection in acute ischemic stroke.

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The Use of Nanotechnology to Improve the Neuroprotective Effects of Adenosine in Stroke and Spinal Cord Injury

There remains a significant need to develop successful pharmacological neuroprotective agents for the treatment of

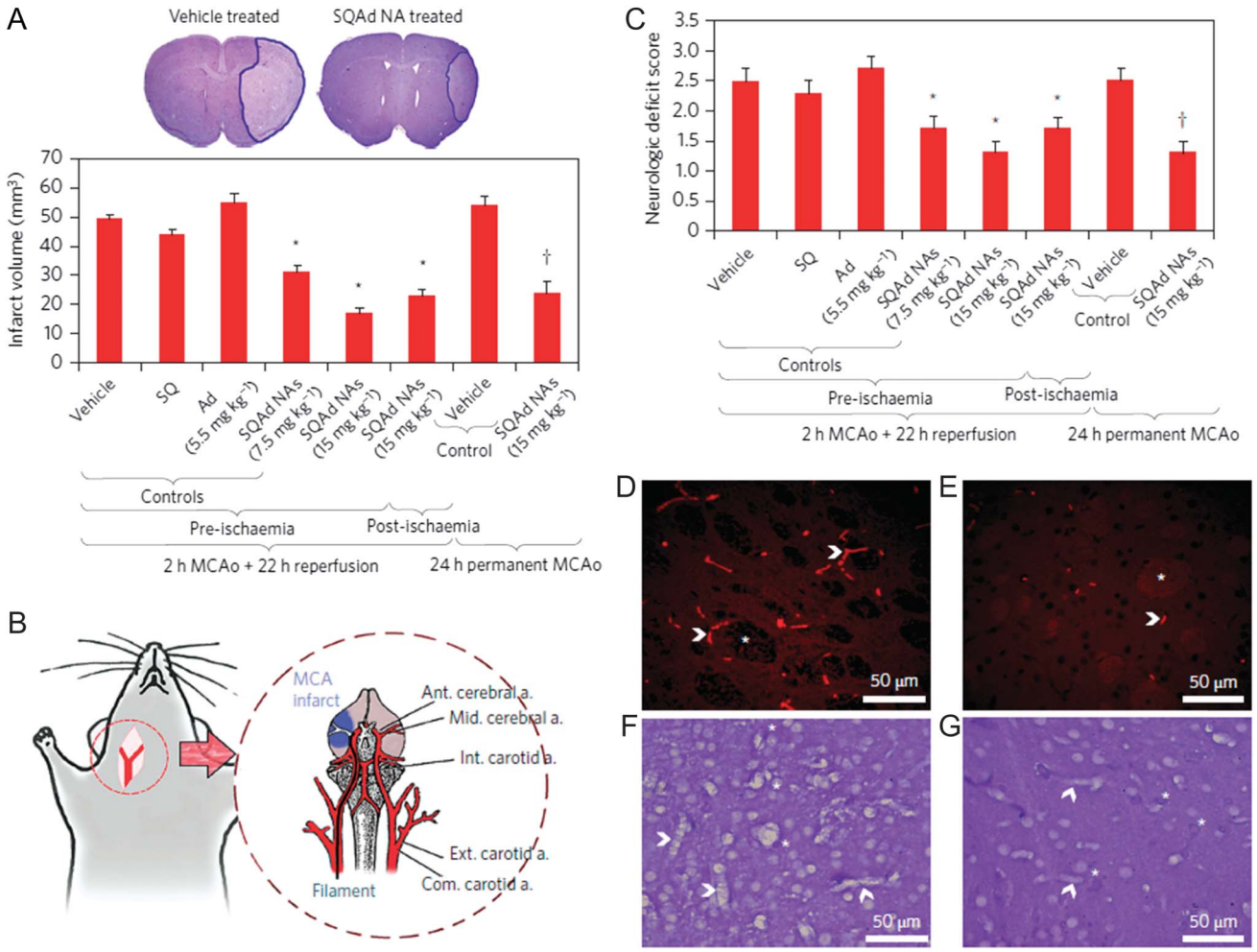

Figure. Systemic administration of squalenoyladenosine (SQAd) nanoassemblies (NAs) provides significant neuroprotection in a mouse model of cerebral ischemia. **A**, *ischemic volumes in control and treated mice subjected to transient (2 hours of middle cerebral artery occlusion [MCAo] and 22 hours of reperfusion) and permanent (24 hours of MCAo) focal cerebral ischemia were identified by reduced Nissl staining under a light microscope.* **B**, *MCAo was performed in mice under anesthesia by the intraluminal filament method.* **C**, *the significant neuroprotective effect of SQAd NAs was also evident in neurological evaluation.* **D** *and* **E**, *in untreated mice, capillaries in the ischemic brain were filled with trapped erythrocytes 6 hours after reopening of the MCA after 2 hours of occlusion, whereas the majority of capillaries were not clogged in SQAd NA–treated mice (***E***). The treatment also reduced ischemic tissue changes such as swelling of axon bundles (***E***, asterisk).* **F** *and* **G**, *the capillary structure was well preserved in treated animals (***G***), unlike in controls (***F***), in which astrocyte end feet ensheathing capillaries and endothelial nuclei were swollen (arrowheads), in addition to edematous neuropil and several dark-stained degenerating cells surrounded by swollen end feet (***F***, asterisks). In treated mice, parenchymal ischemic changes were mild (***G***, asterisks). Reprinted by permission from Macmillan Publishers Ltd: Nature Nanotechnology (Gaudin A, Yemisci M, Eroglu H, et al. Squalenoyl adenosine nanoparticles provide neuroprotection after stroke and spinal cord injury. Nat Nanotechnol. 2014;9(12):1054-1062. doi: 10.1038/nnano.2014.274. [Epub ahead of print]), copyright (2014).*