Experimental treatments for poststroke disability
Hasten slowly

Sometimes, patients just want us to fix them. In an era of robot-assisted technology and virtual reality, when we hear stories about miraculous recoveries and the seemingly boundless plasticity of the human brain, people are often baffled by the existence of ongoing disability after brain injury. It would be a rare neurologist who has not had a family member attend clinic clutching a stack of printed Internet pages and lamenting the fact that as a society we have been able to put a man on the moon but we cannot fix her or his mother.

The science of rehabilitation continues to evolve.\(^1\) Rehabilitations accounts for around one third of the cost of stroke care, but we remain unsure of how or even if it works.\(^2\) Researchers in rehabilitation have called for a shift to an emphasis on understanding the mechanisms of neurologic plasticity and how we can harness these for individual recovery.\(^2,4\) This will lead to many potential new therapies, both physical and pharmacologic. Researchers who lived through the age of neuroprotection—and its associated failures and lessons—may be forgiven for some circumspection, but the prospect of new therapies from unexpected sources is an exciting one. Patients are keen—at times, desperate—to participate in these experimental studies, even if they are not fully appraised of the potential risks or lack of benefit.

An ischemic stroke triggers a complex interplay of events, both locally and remotely. Some effects, such as the microglial-modulated inflammatory cascade, may have neuroprotective benefits but may inhibit native mechanisms of recovery. Some researchers believe that cytokine-mediated elements of this inflammatory reaction cause secondary harms, exacerbating poststroke disability. Many have posited tumor necrosis factor (TNF) as a potential target for intervention. Highly efficacious TNF-α blockers exist, such as etanercept, developed for the treatment of rheumatoid arthritis.\(^5\) Etanercept is an engineered dimeric fusion protein, and its proponents have championed its use for many other conditions, including poststroke disability and dementia.\(^6\)

Gronseth and Messé\(^6\) were tasked by the American Academy of Neurology to examine the evidence for the use of etanercept in reducing poststroke disability, and present their report in this issue of Neurology\(^9\). They identified only 2 case series. The first consisted of 3 patients treated off-label with perispinal etanercept 13, 35, and 36 months following their acute stroke.\(^6\) The study reported significant clinical improvements in all 3 patients, evident within 10 minutes of the first injection. The second study was a chart review of 617 chronic stroke patients treated with perispinal etanercept 0.5–419 (mean 42.0 ± 57.8) months after stroke. In this study, the authors reported substantial improvements in motor impairment, spasticity, sensory impairment, cognition, psychologic function, aphasia, and pain, regardless of the duration between stroke onset and treatment.\(^7\)

The scientific rationale for these studies has limitations. The central belief is that inflammatory response after stroke is detrimental to recovery, and that inhibiting this response can prevent further injury.\(^8\) This is not supported by recent literature, which suggests that microglial activation also facilitates recovery, and that suppressing inflammation may be detrimental to longer term outcomes.\(^7\) The emerging picture is that of inflammation having both a beneficial or detrimental effect on recovery depending on the stage of stroke, with important implications for modulating interventions.

The stroke penumbra resolves in a few weeks, inflammation diminishes considerably in a few months, and reorganization occurs over a longer period, usually within 12–18 months of stroke.\(^9\) It is also worth reminding that the effectiveness of anti-inflammatory treatments for acute stroke seen in animal models have not been replicated in clinical trials.\(^10\) Against this context, there is no convincing explanation in either article for why such an extensive, consistent, and rapid effect was seen on average 3 and a half years after stroke onset, despite dampening inflammatory responses.

There were also limitations to the design of these studies and the validity of the measures used. A control population was not included in either study. It is possible that some of the observed improvement could be attributed to natural recovery or a placebo.
effect of the intervention. The outcome measures used were highly subjective, arbitrary, and assessed by observers not masked to intervention. There are also concerns about the approach used to evaluate patient outcomes and the precision of the tools used to measure improvements. Specifically, the treating physician or nurse practitioner from the authors’ clinics judged participants to be improved or not improved in several domains of impairment, and there is little detail on the actual levels of impairment exhibited by persons before intervention, or the ways in which the intervention ameliorated impairment following its provision.

Hence, it is no surprise that both studies were rated as Class IV evidence on the basis of poor scientific and methodologic quality. The authors found there is insufficient evidence to support or exclude the use of etanercept as an agent for the treatment of poststroke disability, and conclude that patients should be counselled regarding these findings, emphasizing potential harms. This is useful information for practitioners, and will provide a useful counterpoint for patient and family discussions. As clinicians, we are always on the lookout for new treatments for our patients, cognizant of a stroke literature littered with early hope and clinical failures. It is premature to dismiss anti-inflammatory treatments for poststroke disability, but it is clear that the current evidence is too slim to provide a basis for recommendation. As it is so often the case in stroke rehabilitation trials, we must hasten slowly, gathering evidence from ongoing trials and developing future studies to understand the underlying science and mechanisms of stroke recovery.

**STUDY FUNDING**
No targeted funding reported.

**DISCLOSURE**
Brodtmann and Kalra are members of the Neurology editorial board. Go to Neurology.org for full disclosures.

**REFERENCES**