AAN Summary of Practice Advisory for **Clinicians**

Practice Advisory: Etanercept for Poststroke Disability

This is a summary of the American Academy of Neurology (AAN) practice advisory, "Etanercept for Poststroke Disability," which was published in *Neurology*® online on June 6, 2016, and appears in the June 7, 2016, *Neurology* print issue.

Please refer to the full practice advisory at *AAN.com/guidelines* for more information, including the definitions of the classifications of evidence and recommendations.

Stroke is a leading cause of major disability.[1] An inflammatory response may play an important role in ischemic stroke.[2] Some authors have hypothesized that the cytokine tumor necrosis factor (TNF) may play a role in the mediation of inflammatory changes in the ischemic penumbra.[3] Etanercept, a fusion protein consisting of the TNF receptor and the Fc portion of immunoglobulin G, inhibits TNF, thereby diminishing neurotoxic TNF-mediated microglia activation that might contribute to poststroke disability.[4] Moreover, anti-TNF-α blockade has been reported to demonstrate efficacy in stroke animal models.[5]

For adult patients with poststroke disability, does etanercept administered by any route (compared with no etanercept or placebo) improve functional status?

Level U	Clinicians should counsel patients considering etanercept for treatment of poststroke disability that there is insufficient evidence to determine its effectiveness and that the treatment may be associated with adverse outcomes and high cost.

Clinical Context

[The practice advisory authors] have very low confidence in the evidence for efficacy of etanercept for poststroke disability because of the high risk of bias of the relevant studies. The biological plausibility of benefit was judged to be low because of the reported immediate onset of benefit and single administration of a transiently acting medication. Explanations other than the effectiveness of the treatment for the observed improvements include observer expectation,[11] performance motivation,[12] regression to the mean,[13] and the placebo effect.[14]

Although adverse events of etanercept were not described in these studies, serious adverse events are described in studies of patients receiving etanercept for other conditions.[15] Such events include injection site reactions, reactivation of tuberculosis, reactivation of hepatitis B virus infection, congestive heart failure, demyelinating neurologic disorders, vasculitis, and hematologic disorders such as aplastic anemia and pancytopenia. A recent randomized trial of subcutaneous etanercept 50 mg once weekly for 24 weeks for the treatment of Alzheimer disease reported no significant difference in the adverse event rates between patients treated with placebo and patients treated with etanercept.[16] However, the study lacked the statistical precision to exclude uncommon, potentially serious adverse events. It is unclear whether the adverse event profile resulting from the recurrent use of etanercept can be generalized to the time-limited perispinal administration used for the treatment of poststroke disability. Given the limitations of the efficacy of the evidence and the potential for serious adverse events, [the practice advisory authors] judge the risk-benefit tradeoffs of etanercept for poststroke disability to be unfavorable.

As of this writing, the cost of a 25-mg vial of etanercept is about $440 in US currency.[17] Additional costs associated with the pretreatment evaluation and administration of perispinal etanercept are likely to be substantially higher.

©2016 American Academy of Neurology

References

1. Murray CJ, Atkinson C, Bhalla K, et al. US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 2013;310:591–608.
2. Tuttolomondo A, Di Raimondo D, Di Sciacca R, et al. Arterial stiffness and ischemic stroke in subjects with and without metabolic syndrome. Atherosclerosis 2012;225:216–219.
3. Clark IA, Alleva LM, Vissel B. The roles of TNF in brain dysfunction and disease. Pharmacol Ther 2010;128:519–548.
4. Tobinick E. Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease. Curr Alzheimer Res 2012;9:99–109.
5. Tuttolomondo A, Pecoraro R, Pinto A. Studies of selective TNF inhibitors in the treatment of brain injury from stroke and trauma: a review of the evidence to date. Drug Des Devel Ther 2014;8:2221–2238.
11. Sackett DL. Bias in analytic research. J Chron Dis 1979;32:51–63.
12. Maclean N, Pound P. A critical review of the concept of patient motivation in the literature on physical rehabilitation. Soc Sci Med 2000;50:495–506.
13. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005;34:215–220.
14. Friedman JH, Dubinsky R. Patient page. The placebo effect. Neurology 2008;71:e25–e26.
15. Senabre-Gallego JM, Santos-Ramírez C, Santos-Soler G, et al.; AIRE-MB group. Long-term safety and efficacy of etanercept in the treatment of ankylosing spondylitis. Patient Prefer Adherence 2013;7:961–972.
16. Butchart J, Brook L, Hopkins V, et al. Etanercept in Alzheimer disease: A randomized, placebo-controlled, double-blind, phase 2 trial. Neurology 2015;84:2161–2168.
17. GoodRx Web site. *http://www.goodrx.com/enbrel?gclid=CPnW68HPzroCFU9o7AodAAgAHA#/?filter-location=Enter+your+ZIP+code&coords=&label=Enbrel&form=syringe&strength=25mg&quantity=custom&qty-custom=5*. Accessed on December 7, 2015.

This statement is provided as an educational service of the American Academy of Neurology. It is designed to provide AAN members with evidence-based guideline recommendations to assist the decision making in patient care. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, and are based on all of the circumstances involved. Physicians are encouraged to carefully review the full AAN guideline so they understand all recommendations associated with care of these patients.

The AAN develops these summaries as educational tools for neurologists, patients, family members, caregivers, and the public. You may download and retain a single copy for your personal use. Please contact *guidelines@aan.com* to learn about options for sharing this content beyond your personal use.

American Academy of Neurology, 201 Chicago Avenue, Minneapolis, MN 55415
Copies of this summary and additional companion tools are available at *AAN.com* or through AAN Member Services at (800) 879-1960.