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Practice advisory: Etanercept for poststroke disability

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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See commentary "[Experimental treatments for poststroke disability: Hasten slowly](#)," on page 2122.

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Abstract

Objective:

To review evidence regarding the effectiveness, safety, and tolerability of etanercept used to treat patients with poststroke disability.

Methods:

We searched MEDLINE and the Cochrane Central Register of Controlled Trials for studies of adult patients with poststroke disability treated with etanercept in order to improve their functional status. We rated each study for risk of bias (Class I–IV) using the American Academy of Neurology therapeutic classification of evidence scheme. Practice recommendations were formulated on the basis of the strength of the evidence and assessments of potential benefits, potential harms, and patient preferences.

Results:

Two case series were identified, and both reported clinical improvements 3 weeks following treatment across a wide range of functional domains. However, both studies were rated Class IV because of poor methodologic quality (i.e., high risk of bias).

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Conclusions:

For patients with poststroke disability, the evidence is insufficient to support or refute a benefit of etanercept for the treatment of poststroke disability.

Recommendations:

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

Several members of the American Academy of Neurology (AAN) approached the AAN's Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) (see appendices e-1 and e-2 on the *Neurology*® Web site at Neurology.org) asking for guidance regarding the use of etanercept for the treatment of poststroke disability.

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

This practice advisory addresses the following question: For adult patients with poststroke disability, does etanercept administered by any route (compared with no etanercept or placebo) improve functional status?

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DESCRIPTION OF THE ANALYTIC PROCESS

In developing this practice advisory, we used the methodologies described in the 2011 edition of the AAN's guideline development process manual as amended, including the process for developing practice advisories.⁶

In June 2013 and again in June 2015, we performed a search of MEDLINE for articles published using the search terms "cerebrovascular disorders" and "etanercept." Search results were filtered through the broad therapeutic clinical query (see appendix e-3 for the specific search strategy employed). The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials were also searched. A secondary search of the references of selected articles and review articles was performed to identify studies missed by our search strategy.

The titles and abstracts of the identified citations were reviewed for relevance to the clinical question. The full text of potentially relevant articles was retrieved and included in the analysis if the investigators determined functional status in patients with stroke who were treated with etanercept administered by any route. Studies in animals and those with non-English-language abstracts were excluded from the analysis. Both authors, along with members of the AAN GDDI, independently reviewed articles and completed data abstraction forms. Discrepancies were resolved through discussion.

The investigators determined acceptable effect measures to be a change from pretreatment status after etanercept treatment on any measure of functional ability. When possible, 95% confidence intervals (CIs) were used as the measure of statistical precision.

Studies were rated for their risk of bias using the AAN 4-tiered classification of evidence scheme for therapeutic studies (appendix e-4). After anchoring to the risk of bias rating, we rated our overall confidence in the evidence using a modified Grading, Recommendations Assessment, Development and Evaluation process (appendix e-5). Subsequently, we developed the wording of actionable recommendations and determined the strength of the recommendations after considering the strength of evidence and deductive inferences, risks and benefits, cost, feasibility, and patient preferences (appendix e-6).

A draft of the practice advisory was made available for public comment from January 28, 2014, through February 28, 2014. The draft manuscript was modified in response to some of the comments.

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ANALYSIS OF EVIDENCE

Our search strategy identified 33 citations. Twenty-nine articles were excluded because they were review articles, did not specifically include patients with stroke, or were performed on animals. We reviewed the full text of 4 potentially relevant articles. One of these articles was a review without primary data,⁷ and one article was a case report of a patient without MRI evidence of a stroke.⁸ Two articles met inclusion criteria.^{9,10}

Study design.

Both studies were nonmasked retrospective chart reviews that included patients with poststroke disability who received etanercept; one of the studies⁹ included 3 patients with stroke who were consecutively treated, and the second study included 617 patients with stroke.¹⁰ Because of the open-label design and absence of a control group, both studies were rated Class IV for a high risk of bias.

stroke. Because of the open label design and absence of a control group, both studies were rated Class IV for a high risk of bias.

It is unclear whether the 3 patients in the first study were excluded in the second study. Thus, additional study descriptions will be limited to the larger study.

Patient characteristics.

The average age of patients described in the larger study was 65.8 years (1 patient was younger than 18 years). The average time since the stroke was 42 months (range 0.5–419). Twenty-seven percent of the patients had hemorrhagic strokes. No standard measures (e.g., modified Rankin Scale score) were provided on the distribution of poststroke disability. The average time of the patients to walk 20 meters was 57.2 seconds (SD 52.52).

Intervention.

All patients were treated with posterior cervical perispinal muscle injections of 25 mg of etanercept followed by Trendelenburg positioning. This approach was based on findings from a rabbit model that suggested perispinal administration results in rapid delivery of large molecules such as etanercept into the CSF through the Batson plexus.⁵

Efficacy.

In the larger study, outcomes were presented immediately posttreatment and after 1 and 3 weeks. Fourteen efficacy measures were presented without a description of prespecified primary or secondary outcomes of interest. These measures included a 20-meter timed walk, a visual analogue pain assessment, left- and right-hand grip strength, the FAS verbal fluency test, and dichotomous outcomes of improved vs not improved in multiple functional domains (global clinical improvement, motor impairment, spasticity, walking impairments, cognitive impairment, psychologic impairment, sensory impairment, aphasia, and pain). Overall, patients demonstrated significant improvements on all outcome measures, including the immediate posttreatment period measured within minutes after etanercept administration. The patients' 20-meter walking speed immediately improved by 7.5 seconds (95% CI 5.5–9.5) on average. The percentage of patients immediately improving in the functional domains ranged from 50.2% (95% CI 44.3%–56%) for pain to 99.3% (95% CI 98.3%–99.7%) for global clinical improvement. Three-week outcomes were presented in a subset of patients. Improvement was maintained in the majority of these patients on all outcomes at 3 weeks (appendix e-5). Anecdotal instances of benefits sustained more than 3 weeks were described.

Safety and tolerability.

Neither study described adverse events following the administration of etanercept.

Conclusion.

Because of the high risk of bias in the available studies, there is insufficient evidence to support or refute the efficacy of perispinal etanercept for the treatment of poststroke disability (2 Class IV studies).

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PUTTING THE EVIDENCE INTO A CLINICAL CONTEXT

We 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 (appendix e-5). 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, we 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.

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RECOMMENDATION

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 (Level U).

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RECOMMENDATIONS FOR FUTURE RESEARCH

Research is needed on the effects of etanercept on poststroke disability. To minimize the risk of bias, future studies of etanercept for the treatment for poststroke disability should randomly allocate patients in a masked fashion to active and placebo treatment arms and employ masked, standardized poststroke disability outcome measures.

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GLOSSARY

AAN American Academy of Neurology

CI confidence interval

GDDI Guideline Development, Dissemination, and Implementation Subcommittee

TNF tumor necrosis factor

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Footnotes

Supplemental data at Neurology.org

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AUTHOR CONTRIBUTIONS

Dr. Gronseth: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Messé: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

G. Gronseth serves as an associate editor for *Neurology* and as an editorial advisory board member of *Neurology Now*, and receives compensation from the American Academy of Neurology (AAN) for work as the chief evidence-based medicine methodologist. S. Messé is the vice-chair of the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN; has received consulting fees from GlaxoSmithKline for protocol development; has received research support from GlaxoSmithKline, W.L. Gore & Associates, and the NIH for clinical trials; and has received royalties from UpToDate for published articles. Go to Neurology.org for full disclosures.

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