Etanercept

An Epidural Steroid Alternative for Minimally Invasive Treatment of Radiculitis

THE treatment of sciatica remains an elusive target. There have been few recent innovations and increasing pressures from insurers and advocates of evidence-based medicine to prove the efficacy of available treatments. Even generally accepted treatments for sciatica have been challenged by large multicenter trials evaluating conservative and operative treatments, such as the SPORT trial.1 This study demonstrated that sciatica symptoms resolve in most patients regardless of treatment allocation, although surgical discectomy patients recover sooner. In the SPORT trial, the surgical group no longer had a significant benefit over conservative therapy at 3 to 6 months based on work status, however, Oswestry Disability scores favored surgery. It is this work-related disability and chronic back pain that lead to such large scale human and economic losses for the industrialized world.

Studies suggest that epidural steroid injections produce, at best, a few weeks of clinical improvement, without a reduction in surgery or sustained improved function.2 Indeed, some guidelines, such as those of the American Academy of Neurology’s Technology Assessment Committee,3 suggest that we should curtail the provision of epidural steroid injections for sciatica. Because side effects limit corticosteroid dosing to no more than a few times per year, it is appropriate to investigate alternatives to epidural steroids if the right candidate treatments emerge. In this issue of ANESTHESIOLOGY, Cohen et al.4 present the first prospective evaluation of etanercept, a tumor necrosis factor-alpha (TNF-α) inhibitor applied perineurally to treat sciatica in humans.

Etanercept is one of several disease-modifying anti-rheumatic drugs that include infliximab and several others. Etanercept is a dimeric fusion protein of a soluble TNF-α receptor to the Fc component of human immunoglobulin G1. This large (150 kDa) molecule binds TNF-α and renders it biologically inactive. Laboratory studies support the role of TNF-α in the pathogenesis of sciatica, suggesting that this mediator of inflammation is a potential therapeutic target.

Olmarker et al.5 were the first to suggest that nucleus pulposus homogenates produced histologic and neurophysiologic changes in cauda equina nerves. Igarashi et al.,6 demonstrated that TNF-α application to the dorsal root ganglion produced similar effects to those seen with nucleus pulposus material. Later studies produced compelling evidence that TNF-α inhibitors reversed neural inflammation and nerve conduction deficits induced by nucleus pulposus material, thus implicating TNF-α and other cytokines as a cause of radiculitis.7 Further studies showed that rat dorsal root ganglia treated with neurotoxic TNF-α reverted to normal when treated with soluble TNF-α receptor-protein aggregates.8

These preclinical experiments eventually led to human clinical trials. In the first studies, both systemically administered infliximab and etanercept were efficacious in the treatment of sciatica in open-label trials9,10. However, a randomized controlled trial of systemic infliximab did not substantiate the improvement noted in the open label studies.11 Cohen et al. have speculated that the failed randomized controlled trial might have been the result of insufficient drug availability locally at the dorsal root ganglion, the site of nerve and disc pathology.

Therefore, Cohen et al.,4 injected etanercept via the transforaminal epidural route. In this study, they compared three groups of six patients who received etanercept in escalating doses. Two patients in each group received sham saline injections (3:1 ratio). Concurrent animal studies were conducted to assess for histologic changes and functional deficits in beagle dogs treated with perineural etanercept. This is an important step because investigations of neuraxially administered compounds require preclinical safety testing. For example, clonidine, a drug that is now commonly used as an adjunct to peripheral nerve block and neuraxial analgesia, had been extensively safety tested in several animal species.12 Only after these studies demonstrated no histologic damage or neurologic deficits were open label and prospective trials conducted, ultimately resulting in Food and Drug Administration approval for epidural administration in cancer neuropathic pain. Another neuraxially administered drug, midazolam, was introduced to patients before the requisite studies had resolved conflicting animal toxicity reports. Neuraxial midazolam studies led to strong criticism from safety experts working in the area of neuraxial administration of novel pharmacotherapies to humans.13

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After the initial phase of this epidural etanercept study, the authors were advised of the need for an investigational new drug requirement for non-Food and Drug Administration approved drugs for neuraxial administration. The human study was temporarily halted until patients who had been studied to date received magnetic resonance imaging showing absence of pathology, and screening magnetic resonance imaging procedures were then mandated for subsequent patients.

Efficacy of perineural etanercept is impossible to determine on the basis of this preliminary safety study because the number of patients treated is very small. Perhaps this small number is the reason that the study by Cohen et al. did not show a dose-response relationship with increasing doses of the active agent. This is troublesome because the mechanism of binding and inactivation of TNF-\(\alpha\) suggests that there should be a dose response. There was very little difference in Oswestry Disability numerical improvement, particularly in the higher-dose etanercept group as compared to saline. Furthermore, those patients with saline treatment had greater disease severity as judged by their baseline Oswestry Disability ratings and pain scores; thus, the sham group had to have greater improvement than did the etanercept groups. Even so, one patient in the saline control group of six had sustained improvement. Many of these limitations can perhaps be overcome by a much larger clinical trial.

So, what are the risks with epidural etanercept? First, etanercept is a large molecule that carries warnings of significant risks for anaphylaxis, immune deficiency, sepsis, tuberculosis (reactivation or novel infection), and the rare possibility of lymphoma. The drug had a black box warning placed in May 2008 by the Food and Drug Administration because of the potential for several adverse occurrences.\(^{14,15}\) Thus, use of etanercept must be weighed against these risks. To understand the true incidence of infections of the neuraxis would likely require thousands of applications of these drugs over many years to compare them to steroids, for instance. Second, the high incidence of sciatica worldwide mandates a safe therapy, because of the potential for hundreds of thousands of yearly injections, provided that future trials of etanercept prove effective. Third, complications from transforaminal etanercept injections might not necessarily require a histopathological process. Witness the relatively recent reports of catastrophic occurrences related to particulate steroid transforaminal injections. Despite several reports of spinal cord and brain infarctions from epidural steroids, we do not know with certainty what causes this problem.\(^{16}\) What might happen if etanercept were inadvertently injected into a radicular artery? Cohen et al. do not comment on safety measures they took to eliminate possible injection errors, and they did not submit to blinded review of fluoroscopic images. Fourth, for all of their faults, the drugs that etanercept might replace, corticosteroids, have a six decade history of use in the epidural space with still relatively few permanent adverse outcomes. Finally, other anticytokine drugs with better safety profiles could emerge. For instance, animal and some human studies suggest that clonidine might have anticytokine effects.\(^{17}\) Clonidine is currently being investigated for perineural administration in sciatica patients.\(^{9}\) It is likely that drugs blocking TNF-\(\alpha\) and other similar candidate compounds could emerge as potential treatments for sciatica.

On the basis of this small numbers of subjects, the reader is strongly cautioned about attempting to inject this drug until further studies have been performed. Although no toxic effects were observed in beagles and no obvious untoward magnetic resonance imaging abnormalities were seen in humans, epidural etanercept requires further extensive evaluation in controlled clinical trials with proper regulatory oversight to prove efficacy and alleviate fears related to its neuraxial administration before clinical use is adopted.

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References
