Thalidomide Has Activity in Treating Complex Regional Pain Syndrome

Rajkumar et al1 reported that thalidomide (Thalomid; Celgene Corporation; Warren, NJ), prescribed for newly diagnosed multiple myeloma, led to unexpected improvement and near resolution of reflex sympathetic dystrophy in a woman with a 3-year history of the disorder. We report on our recent clinical experience using thalidomide to treat reflex sympathetic dystrophy, better known as complex regional pain syndrome (CRPS). This disorder is characterized by neuropathic pain, allodynia, edema, autonomic dysfunction, disordered movements, dystrophy, and atrophy.2

Independently, we treated 42 patients who satisfied the International Association for the Study of Pain definition of CRPS with thalidomide.3 Institutional review board approval was obtained at 2 institutions (Mayo Clinic, Rochester, Minn [K.B.], and St Elizabeth’s Hospital, Youngstown, Ohio [E.C.]); at the third institution (Drexel University College of Medicine, Philadelphia, Pa [R.J.S.]), informed consent was obtained from all study participants according to the Declaration of Helsinki. All patients had long-standing disease, in whom multiple previous interventions had failed. To ensure the safe use of thalidomide, all patients followed the System for Thalidomide Education and Prescribing Safety (STEPS) program.4 Although the starting dose of thalidomide varied, most patients initially received 200 mg daily and were titrated over several weeks to 300 to 400 mg daily, the same regimen used by Rajkumar et al.1

Both objective and subjective responses were observed, including increased function, healing of dystrophic lesions, pain reduction, and lower analgesic requirements. “Dramatic responses” occurred in 7 (17%) of the 42 patients treated with thalidomide. In addition, 6 patients (14%) experienced at least modest pain relief and/or showed some reduction in the need for concurrent pain medications, specifically those used to treat breakthrough pain. Treatment responses were usually evident within 4 to 6 weeks of starting thalidomide therapy, with deep joint pain and allodynia generally being the first symptoms to improve. Skin lesions and inflammatory skin changes also improved dramatically in some patients, consistent with the case report by Rajkumar et al.1

Patients often felt worse during the first few weeks of therapy, specifically with increased pain and edema. Rash, somnolence, and constipation were the most common adverse effects that patients reported. The rash was typically mild, transient (resolving in a few days to weeks), and without clinical significance. Somnolence, while intolerable to some, was actually of benefit to many patients. It is important to note that having CRPS does not preclude a significant beneficial response to thalidomide therapy.

The observed clinical activity of thalidomide in our difficult-to-treat patients with CRPS is significant, given the inherent challenges of treating this disorder. Thalidomide is currently approved for use in short-term treatment of moderate to severe erythema nodosum leprosum and in maintenance therapy for preventing recurrence of the cutaneous manifestations of erythema nodosum leprosum.5 Thalidomide has also shown promising activity in multiple myeloma and a number of other malignancies and immunologic disorders. Among its mechanisms of action, thalidomide inhibits production of tumor necrosis factor α and other cytokines. Tumor necrosis factor α and interleukin 6 were recently detected at significantly higher levels in suction blister fluid collected from the involved extremity of patients with CRPS compared with the noninvolved extremity.6 Although the role of these cytokines in CRPS is not entirely clear, the cytokines may directly depolarize C and Aδ afferent pain fibers or reduce their threshold for firing; alternatively, they may contribute to the inflammatory features of the disorder.2,7

A controlled, randomized, multicenter study is being planned to evaluate more fully the activity of thalidomide in CRPS and other inflammatory neuropathies. In the meantime, if thalidomide therapy is considered, physicians need to address patients’ expectations and counsel them about the potential adverse effects as well as benefits of treatment.

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We are pleased that studies by Schwartzman et al confirm our initial case report describing the complete resolution of reflex sympathetic dystrophy (or CRPS) with thalidomide therapy. The patient we described is doing well and continues to receive thalidomide for the treatment of myeloma at a maintenance dose of 100 mg/d. With a current follow-up of 30 months, she remains asymptomatic and has no recurrence of CRPS. We fully concur with the plan by Schwartzman et al to initiate a multicenter, randomized trial to further define and establish the role of thalidomide for this serious and disabling condition.

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Literature Reports of Angiotensin Receptor Antagonist-Induced Angioedema in Patients With a History of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema

It was with grave concern that I read a recent case report by Drs Gavras and Gavras in the January 27, 2003, issue of the Archives. Their report described no incidents of angioedema following the use of angiotensin receptor antagonists (ARBs) in 10 patients who had previously incurred angioedema secondary to the use of angiotensin-converting enzyme (ACE) inhibitors. Their case report omitted numerous findings from the literature, and as a result the authors’ conclusion is dangerously misleading.

The authors stated that they were “not aware of any report about patients who developed angioedema while receiving ACE inhibition and who were subsequently treated with an ARB.” The fact of the matter is that numerous such cases have been reported, the first in 1996 by Boxer. One of these studies reported that from a group of 13 patients known to have angioedema caused by ARB use, 3 had a history of angioedema caused by ACE inhibitor use. These reports can all be found through MEDLINE and other literature search engines and should be included in any discussion of ACE inhibitor and ARB-induced angioedema.

Angioedema can be life threatening. The fact that some patients with ACE inhibitor–induced angioedema also subsequently developed angioedema from ARB use makes ARB therapy potentially dangerous in any patient with a history of ACE inhibitor–induced angioedema. While it provides hopeful data, unfortunately the report from Drs Gavras and Gavras does not alleviate concerns of using ARBs in patients with a history of ACE inhibitor–induced angioedema. Caution is advised in these situations.

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Angioedema and AT1 Receptor Blockers: Proceed With Caution

I am writing in response to the case report of Drs Gavras and Gavras titled “Are Patients Who Develop Angioedema With ACE Inhibition at Risk of the Same Problem With AT1 Receptor Blockers?” The authors report a small sampling of patients who had angioedema with ACE inhibition, but who subsequently tolerated ARB medications without adverse effects. They state that there findings “should alleviate the concerns of physicians who may be reluctant to use an ARB in such patients, despite anticipated benefits.” Further, they state, “We are not aware of any report about patients who developed angioedema while receiving ACE inhibition and who were subsequently treated with an ARB.” A search of the literature would suggest otherwise. In the Archives in 1998, Van Rijnsoever et al reported 13 cases of angioedema in patients taking losartan. Three of these individuals had previously reported angioedema while using an ACE inhibitor. Warner et al reported that 32% of individuals who experienced angioedema with ARB use had experienced a prior episode of angioedema attributed to ACE inhibitor therapy. In a review of the safety of ARB use in patients with ACE-induced angioedema, Howes and Tran state that “angiotensin receptor antagonists cannot be considered to be a safe alternative therapy in patients who have previously experienced ACE inhibitor-associated angioedema.” The incidence of angioedema in patients taking ARBs is clearly lower than that seen with ACE inhibitors. However, the use of ARBs in patients who have previously experienced angioedema with ACE inhibitors should be undertaken with caution.

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