Improvement of Postherpetic Neuralgia After Treatment With Intravenous Acyclovir Followed by Oral Valacyclovir

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Background: Postherpetic neuralgia (PHN) is a complication of shingles (herpes zoster), a painful rash due to varicella-zoster virus reactivation. Studies of patients with PHN and zoster sine herpete (radicular pain without rash) support the notion that low-grade viral ganglionitis contributes to pain. If chronic pain reflects active infection, then antiviral therapy may help patients with PHN.

Objective: To determine whether antiviral treatment helps reduce PHN-associated pain.

Design: Prospective, open-label phase I/II clinical trial.

Setting: Tertiary care university hospital.

Patients: Fifteen patients with moderate to severe PHN.

Interventions: Intravenous acyclovir at a dosage of 10 mg/kg every 8 hours for 14 days followed by oral valacyclovir at a dosage of 1000 mg 3 times per day for 1 month.

Main Outcome Measure: Numeric Rating Scale for Pain score.

Results: As defined by a decrease of 2 or more points on the Numeric Rating Scale for Pain, 8 (53%) of 15 patients reported improvement.

Conclusion: Clinical improvement reported by most of our patients warrants further investigation in a larger, randomized, double-blind, placebo-controlled trial.

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Primary infection with varicella-zoster virus causes chickenpox (varicella), after which the virus becomes latent in cranial nerve, dorsal root, and autonomic ganglia along the entire neuraxis. Decades later, virus reactivation produces shingles (herpes zoster), characterized by pain and rash restricted to 1 to 3 dermatomes. Although pain usually resolves within 4 to 6 weeks, more than 40% of patients with zoster who are older than 70 years experience postherpetic neuralgia (PHN), pain that persists for months to years. As many as 1 million Americans are affected.1 Although the cause of PHN is unknown, 2 non–mutually exclusive theories are that the excitability of ganglionic or spinal cord neurons is altered or that low-grade virus infection persists in ganglia. Pathological analysis of ganglia from patients with PHN has revealed diffuse and focal infiltration by chronic inflammatory cells, raising the possibility of prolonged viral infection.2,3 The detection of varicella-zoster virus DNA and proteins in peripheral blood mononuclear cells of patients with PHN4,5 and studies of patients with zoster sine herpete (radicular pain without rash)6,7 further support the notion that low-grade viral ganglionitis contributes to PHN. If chronic pain reflects active infection, then antiviral therapy may help patients with PHN. Although a large double-blind study using intravenous (IV) antiviral drug has been recommended,8 such a trial is time-consuming and expensive. Thus, before undertaking a major study, we first conducted an uncontrolled phase I/II trial to see whether IV acyclovir helped patients with PHN.

METHODS

Written informed consent approved by the Colorado Multiple Institutional Review Board, Aurora, was obtained from each patient. Twelve men...
and 3 women aged 53 to 82 years (median age, 72 years) were treated with IV acyclovir at a dosage of 10 mg/kg every 8 hours for 14 days followed by oral valacyclovir at a dosage of 1000 mg 3 times per day for 1 month. Pain was measured using the Numerical Rating Scale for Pain (NRSP), an 11-point scale in which a score of 0 indicates no pain and 10 indicates worst possible pain.

At enrollment, the median NRSP score was 5 and the median duration of PHN was 12 months (Table). All of the patients had tried or were receiving different combinations of pain medications for PHN, including opioids, tricyclic antidepressants, and gabapentin. Any patient receiving pain medications for PHN continued the same regimen for the duration of the study.

All of the patients met inclusion criteria of being older than 50 years, having PHN lasting more than 3 months, and having an NRSP score of 4 or higher. Exclusionary criteria were any other source of significant pain, allergy to acyclovir, immunosuppression, and a white blood cell count of fewer than $3.5 \times 10^9$/L or a serum creatinine level higher than 106.08 µmol/L (1.2 mg/dL). Patients completed the NRSP questionnaire before receiving acyclovir (day 1), immediately after finishing IV acyclovir (day 15), immediately after finishing oral valacyclovir (day 45), and 1 month after finishing valacyclovir (day 75).

Because a 2-point reduction correlates with clinically meaningful improvement, the primary outcome measure of successful treatment was defined by a decrease of 2 or more points in the NRSP score at the end of the study (day 75). The sample size of 15 patients was chosen to provide sufficient accuracy for estimating the chance that a patient would experience a clinically meaningful decrease in pain. Statistical inference about the success rate used exact methods based on the binomial distribution.

Data were analyzed using a conservative intention-to-treat method. On day 75, the NRSP scores were collected regardless of whether patients finished treatment; patients for whom the data from day 75 were missing were counted as nonresponders. All of the 15 patients were included in the denominator for the calculation of the percentage of patients who had improved.

RESULTS

At the end of the study (day 75), 8 (53%) of 15 patients reported a clinically significant reduction in pain (95% confidence interval [CI], 27%-79%) (Figure). Based on this 95% CI, the response rate was significantly larger ($P<.05$) than 27% and possibly as great as 79%. This improvement was similar to that found at earlier times (day 15 when IV acyclovir treatment was completed and day 45 when oral valacyclovir treatment was completed). On day 15, 7 (47%) of 15 patients reported improvement (95% CI, 21%-73%). On day 45, 8 (53%) of 15 patients reported improvement (95% CI, 27%-79%).

Treatment was well tolerated by most patients. Adverse effects of IV acyclovir were mild and reversible. Two patients were released from the study during IV acyclovir treatment. One was discharged on day 3 because of serum creatinine level elevation that was probably caused by acyclovir since the serum creatinine level normalized after acyclovir was stopped. The second patient received IV acyclovir for 10 days but was terminated from the study owing to a concomitant viral respiratory tract infection complicated by exacerbation of preexisting atrial fibrillation and elevated serum levels of alanine aminotransferase and aspartate aminotransferase. These events were not likely related to acyclovir but necessitated transfer from the research ward to an inpatient medical unit. A third patient withdrew from the study on day 5 because she was unable to tolerate intravenous catheter insertions.

The remaining 12 patients began receiving oral valacyclovir after 14 days of IV acyclovir; 10 patients com-
pleted the 30-day course, and 2 stopped early (one because of unexplained dyspnea and the other because of nausea, fatigue, and malaise). These symptoms disappeared when valacyclovir was discontinued.

Overall, 8 (53%) of the 15 patients who began treatment experienced a noticeable reduction in PHN-associated pain after sequential acyclovir and valacyclovir treatment. Because this was an open-label study with no placebo control, we cannot exclude the possibility that this effect was due to a placebo response or spontaneous improvement. However, based on our clinical experience in treating patients with PHN, a 53% success rate is promising. Such a degree of improvement would be unlikely to occur spontaneously during any 3-month observation period in patients with PHN. Also, our 95% CI analysis indicated that the proportion of improved patients was significantly larger ($P<.05$) than 27%, a reasonable estimate of placebo response. Similar placebo response rates have been reported in other large, multicenter treatment trials of PHN.

Pain is a subjective symptom that is difficult to measure, but most pain treatment trials use the NRSP. Prior analyses of several large clinical trials of chronic pain have shown the correlation of a 2-point or 30% reduction in the NRSP score with clinically meaningful improvement as measured by the widely used Patient Global Impression of Change scale, a 7-point scale ranging in scores from −3 (very much worse) to +3 (very much better). Other commonly prescribed symptomatic treatments for PHN, such as gabapentin, have demonstrated similar average NRSP reductions of 2 points.

Although pain scores improved after IV acyclovir, no additional improvement was apparent after oral valacyclovir; nevertheless, oral antiviral therapy may have provided continued viral suppression while prolonging the period of pain relief. Only 1 other study has examined IV and oral acyclovir as a treatment for PHN. Between September 1983 and December 1984, 10 patients with PHN were treated with antiviral agents, placebo, or both: 5 subjects received IV and oral acyclovir, 2 received IV placebo and oral acyclovir, 1 received IV acyclovir and oral placebo, and 2 received oral and IV placebo. Of the 6 patients with PHN who received IV acyclovir, only 1 reported improvement, and the investigators concluded that IV acyclovir was not beneficial. However, the small number of enrolled patients prevents firm conclusions.

Although our study was small and without placebo control, the findings suggest a promising effect of antiviral treatment on PHN. Overall, patients were recruited without difficulty and treatment was well tolerated. Treatment of PHN with IV acyclovir will be expensive. However, elimination or reduction of pain coupled with reduced burden of disease and use of health care resources could offset treatment costs. Correlation of clinical with virological data in the future may help to clarify the role of persistent viral ganglionitis in the pathogenesis of disease and ultimately provide a means of identifying patients likely to respond to antiviral treatment. Based on our findings, we now believe that a large, randomized, double-blind, placebo-controlled trial is warranted.

**REFERENCES**