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Treatment of Postherpetic Neuralgia With Gastroretentive Gabapentin: Interaction of Patient Demographics, Disease Characteristics, and Efficacy Outcomes

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Abstract: **To understand how patient demographics and patient-reported disease characteristics relate to successful management of postherpetic neuralgia (PHN), integrated data from phase 3 and phase 4 studies of patients with PHN (n = 546) who received once-daily gastroretentive gabapentin (G-GR, 1800 mg) were analyzed. There were widespread, networked, positive correlations among efficacy end points—pain qualities on the visual analog scale (VAS) and Brief Pain Inventory (BPI), measures of pain interference on the BPI, and Patient Global Impression of Change (PGIC)—most likely characterized by positive feedback loops, in which pain interferes with patient functioning, and poor functioning enhances pain. VAS scores at baseline or at week 2 were the strongest predictors of being "much" or "very much" improved on the PGIC; BPI sleep interference scores were the strongest predictors of percent changes in BPI pain qualities and in the average of BPI interference scores, whereas age, sex, and race were not important predictors. In addition to VAS, BPI sleep interference and PGIC assessments appeared to be key co-strategic factors important for successful treatment outcomes, and should be considered as co-primary end points in future clinical trials of PHN. This could improve detection of true positive efficacy responses and guide successful transition to real-world clinical practice.**

***Perspective:** This study describes complex relationships among measures of pain intensity, pain interference with daily activities, and demographics of patients with PHN treated with G-GR. Such comprehensive characterization provides important insight into how different variables contribute to successful treatment, and may lead to better management of neuropathic pain.*

Key words: *Postherpetic neuralgia, neuropathic pain, gabapentin, gastroretentive, pain intensity, pain interference.*

Reactivation of dormant varicella zoster virus, originally contracted in childhood during a chicken pox infection, leads to herpes zoster (or shingles), a painful skin rash with blisters.[19,45] The symptoms of herpes zoster typically resolve within 2 to 4 weeks, but approximately 10 to 20% of patients develop postherpetic neuralgia (PHN), a neuropathic pain condition.[11,28,31,44] PHN is commonly defined as pain persisting for more than 3 months after the healing of the herpes zoster rash, although it can persist for more than a year.[44] Recommended first-line treatment options for PHN include gabapentinoids (various formulations of gabapentin and pregabalin), tricyclic antidepressants, and the topical lidocaine 5% patch.[2,5,13] The gastroretentive formulation of gabapentin (G-GR), approved by the US Food and Drug Administration (FDA) for treatment of PHN, uses a polymer-based technology to swell when the tablets come in contact with gastric fluid, and is retained in the stomach for 8 to

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10 hours,[1,16] allowing for once-daily dosing and a simple 2-week titration regime. In 2 phase 3 placebo-controlled studies and in 1 phase 4 open-label study, once-daily 1800 mg of G-GR provided significant pain relief, significantly reduced pain interference with daily activities, and demonstrated a good safety and tolerability profile in patients with PHN, including in older patients.[12,25,37,43]

Available treatments for PHN focus on shortening the duration and severity of the pain. However, neuropathic pain associated with PHN can be debilitating, and it frequently interferes with patients' physical and social functioning.[4] Therefore, in addition to pain relief, improvement in various aspects of pain interference with patients' daily lives may provide quality patient care and improve patients' overall well-being. Several instruments that measure the effect of treatment on pain intensity and on other pain qualities, as well as on how pain affects various aspects of patients' lives, have been developed and are commonly used in clinical studies of pain therapies.[7] Among these, the visual analog scale (VAS) is among the most frequently used instruments to measure pain intensity.[14] The Brief Pain Inventory (BPI) measures both the intensity of pain (worst, least, average, and current pain) and the interference of pain in 7 aspects of patient's functioning (general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life).[3] The Patient or Clinical Global Impression of Change (P/CGIC) is commonly used to assess overall efficacy and treatment experience.[22]

Pain intensity is the most common primary outcome variable assessed in studies of pain therapies, including in PHN, whereas measures of patients' quality of life and how pain interferes with their functioning are secondary efficacy measures. Because pain frequently interferes with daily activities, measures of pain intensity would be expected to be positively associated with measures of pain interference with patient functioning. Levels of pain intensity and its interference recorded at baseline may influence the effectiveness of treatment. Also, the complexity of pain and its interference with functioning is largely dependent on subjective reporting by patients, and patient demographics (ie, age, sex, or race) may influence self-reporting. Moreover, age, sex, and race have been reported to be differentially associated with the experience of pain,[8,26,34] which may also influence treatment outcomes.

A major risk factor for PHN is advanced age, with approximately half of all PHN cases occurring in patients older than 60 years, and female sex has been reported to be an important risk factor among others.[21,29,44,45] Also, race may influence susceptibility to herpes zoster, thus to subsequent PHN[6,40]; and individual genetic factors may prove important for specifically targeted treatment of neuropathic pain.[38] Therefore, studying relationships among patient demographics, disease characteristics, pain severity, and corresponding levels of pain interference with daily activities can identify factors important for multidimensional treatment of PHN in clinical practice.

Although there are a number of publications describing risk factors for PHN as well as factors that affect pain experience, comprehensive analyses on how various baseline characteristics can influence PHN treatment outcomes have not been performed. Therefore, the goal of the current, secondary analysis of integrated data from the phase 3 and 4 studies of G-GR was to better understand how patient characteristics and key patient-reported outcome measures relate to patients' overall well-being after treatment with G-GR. Such comprehensive analysis may identify factors important for multidimensional responses to treatment that can potentially inform the design and evaluation of treatment strategies for better management of PHN.

Methods

Patients

Data from patients treated with G-GR in 2 phase 3, double-blind, randomized, placebo-controlled studies (81-0045 and 81-0062) and 1 phase 4, open-label, single-arm study (81-0067) were integrated before this analysis. Patients treated with placebo in phase 3 studies were not included in this analysis because this would have resulted in uneven G-GR versus placebo patient populations. Also, various exploratory analyses of integrated data from phase 3 studies for differences between patients treated with G-GR and patients treated with placebo were published previously.[10,12,17,18,33]

The main patient inclusion criteria for the phase 3 studies were age ≥18 years with neuropathic pain for ≥3 months (81-0045) or ≥6 months (81-0062) after the healing of herpes zoster skin rash; and an average daily pain score of ≥4 based on an 11-point Likert scale (where 0 = no pain and 10 = worst possible pain), at the end of a 1-week pretreatment baseline period. Main exclusion criteria included previous lack of response to treatment with ≥1200 mg/day gabapentin or ≥300 mg/day pregabalin; dose-limiting adverse events with gabapentin or hypersensitivity to gabapentin; use of any concomitant medication excluded by the inclusion criteria (including capsaicin, opiates, topical lidocaine, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors); and creatinine clearance (CrCl) <50 mL/min. For the phase 4 study, patients were relatively unselected to reflect the real-world population, and included patients ≥18 years with active PHN, regardless of their baseline pain scores. Exclusion criteria were limited to those in the product label: pregnant women or nursing mothers, patients with hypersensitivity to gabapentin, and patients who had an estimated Cr/Cl <30 mL/min or who were on hemodialysis. There were no restrictions on the use of prior medications in the phase 4 study, and the use of concomitant neuropathic pain medication was permitted.

Treatments

All 3 studies shared a similar G-GR treatment schedule. Patients were titrated to 1800 mg/day G-GR over 2 weeks, followed by 8 weeks (phase 3) or 6 weeks (phase 4) of