EDITORIAL

CGRP — The Next Frontier for Migraine

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Migraine is a common problem for adults and children. In its global burden as a disease, it is consistently in the top 10, and among neurologic disorders, it is second only to stroke in its number of associated disability-adjusted life-years.[1,2] Currently, treatment for migraine involves a multipronged approach of abortive, preventive, and biobehavioral therapies, as well as treatments that have been developed for other diseases, such as antiepileptic medications. The complexity of migraine, which is considered to be a polygenetic disease with environmental modifiers, is the main reason for the paucity of migraine-specific treatments. In the 1980s, the first acute migraine–specific medications — the triptans — were developed, but consistently effective migraine-preventive therapy has proved elusive. That has recently changed.

Calcitonin gene–related peptide (CGRP) is a neuropeptide that, along with its receptor, is located in both central and peripheral neurons (reviewed by Edvinsson[3] and Iyengar et al.[4]). The peptide influences both neuronal modulation of pain and vascular activity. These actions are facilitated particularly by its location in dorsal root and trigeminal ganglions, and it is these dual actions that make its role in causing migraine plausible.[5] Its involvement in the pathophysiological processes underlying migraine led to the development of CGRP antagonists (the "-gepants") and four different antibodies targeting the CGRP receptor (erenumab) or targeting CGRP itself (eptinezumab, fremanezumab, and galcanezumab).

Two phase 3 trials of these antibodies are presented in this issue of the *Journal*. Goadsby and colleagues report on a trial of erenumab, a fully human monoclonal antibody targeting the CGRP receptor for the prevention of episodic migraine,[6] and Silberstein and coworkers present the results of a trial of fremanezumab, a human monoclonal antibody targeting CGRP itself for the prevention of chronic migraine.[7] The International Classification of Headache Disorders (ICHD)[8] defines chronic migraine as 15 or more headache days per month with at least 8 migraine days. In most trials, migraine that is not chronic (i.e., with <15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD. The erenumab trial used a primary end point of a change from baseline in mean migraine days per month (i.e., days with a migraine or on which acute migraine–specific medication was used), and the fremanezumab trial used a primary end point of a mean change from baseline in headache days per month (i.e., days with a headache that was of at least moderate peak severity and had a duration of at least 4 hours or on which acute migraine–specific medication was used). Variability in the definitions of headache frequency among migraine-prevention trials often restricts direct comparison of their results.

In the trial of erenumab for episodic migraine, the results with regard to the primary end point differed significantly between erenumab (at either the 70-mg or the 140-mg dose) and placebo over a period of 4 to 6 months. The decrease in migraine days per month was 1.4 and 1.9 days greater in the 70-mg erenumab group and the 140-mg erenumab group, respectively, than in the placebo group, from a baseline of 8.3 days per month. Although these changes are modest, they indicate efficacy and are consistent with phase 2 studies of CGRP antibodies. The great-

est reduction in migraine days occurred in the first 2 months after treatment initiation, which suggests that a clinical decision about whether the medication is effective can be made quickly. The secondary end point of a 50% or greater reduction in migraine days per month occurred in more than a quarter of the patients in the placebo group and approximately half the patients in the erenumab groups.

In the trial of fremanezumab, the drug was administered either monthly or quarterly for the prevention of chronic migraine; the results with regard to the primary end point differed significantly between either regimen of fremanezumab and placebo. The participants in this trial started with a higher number of total headache days per month than did those in the episodic migraine trial (approximately 20 days with a headache of any kind, with approximately 13 headache days of the type defined for the analysis of the primary end point). The two fremanezumab groups had similar reductions from baseline in the number of headache days, and these reductions exceeded that in the placebo group by approximately 2 days per month, which indicated modest but meaningful efficacy. The most notable improvement was seen after the first injection, again suggesting the potential for a rapid determination of efficacy. A more than 50% reduction in headache frequency occurred in just under 20% of patients in the placebo group, as compared with approximately 40% of patients in both fremanezumab groups.

With the ongoing development of four different antibodies targeting the CGRP pathway, it will be difficult to determine whether unique patient populations will have a response to a specific drug or whether one agent is superior to others. Furthermore, many patients will probably still have a response to standard multidisciplinary treatment that is less costly in patient and provider time and dollars. It is of interest that these agents worked rapidly and that a number of patients became completely headache-free. Thus, these drugs may find a specific role in the treatment of patients who have migraines that are refractory to treatment or who are severely disabled by headaches. For the long term, it will be important to determine whether the beneficial effect can be sustained after discontinuation or whether continued treatment will be necessary.

A migraine-specific preventive treatment that is directed toward a suspected underlying pathophysiological mechanism is an important advance for patients with migraine. As mechanisms of migraine are revealed by advances in neuroimaging, biomarker identification, and genomic analysis, one may expect new compounds to bring a brighter future to our patients who have migraine.

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