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LETTER TO THE EDITOR

CGRP Monoclonal Antibodies for Prevention of Migraine: There are Many Adverse Effects

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This letter is in response to the excellent July, 2020 article "Migraine and CGRP Monoclonal Antibodies: A Review of Cardiovascular Side Effects and Safety Profile" (Boldig and Butala) [1]. There are a plethora of adverse effects (AEs) from the CGRP monoclonals (mAbs) that were not identified in the Phase 3 trials. Unfortunately we frequently encounter this with new drugs. It often takes several years to identify an accurate picture of the adverse effect profile.

The package insert (PI) for the CGRP mAbs, as with many of the new drugs, identifies few AEs. The reasons for this include: 1. trial investigators did not use a checklist of AEs (a checklist is almost never utilized during drug trials) 2. As with most drug trials, the studies were powered for efficacy but would need many more patients to accurately assess AEs 3. The studies do not extend long enough in order to identify the true adverse effect profile and 4. Adverse effects become "disaggregated". For instance, one person may say they have malaise while another may state they suffer from fatigue. This adverse effect is disaggregated and subsequently not included in the PI. After the study is completed these effects may be reaggregated, but that method is not accurate.

To accurately assess AEs post-approval, we must examine multiple lines of evidence. The FDA/FAERS website is an important source of information. Unfortunately, the side effects listed are adverse events, not necessarily adverse effects. As of January 2021, (2.5 years post-launch) there were 40,378 adverse events catalogued from the four CGRP mAbs. On the FDA website, serious adverse events include those that are life threatening, or that resulted in hospitalization. 5,562 serious adverse events were listed. These numbers are staggering, particularly considering that the vast majority of adverse effects, even serious ones, go unreported. Erenumab resulted in the bulk of the adverse events. This is most likely because erenumab was the first to market and has been the CGRP mAb most widely utilized. Save for constipation, I do not believe that erenumab is necessarily more likely to produce adverse effects than are the other 3 mAbs.

After the launch of the drug, another line of evidence is the available post-approval studies and case reports. One of the observational studies concluded that adverse effects resulted in 33% of erenumab discontinuations [2]. Another study described 63.3% of patients as having reported an adverse effect, but they concluded that the CGRP monoclonal antibodies were well tolerated [3]. We published a study of 119 chronic migraine patients who had utilized one of the CGRP monoclonals [4]. We incorporated a checklist of 19 possible adverse effects. The patients were initially asked about adverse effects by posing the question, "Have you experienced any issues, problems, or side effects from the injection?" Subsequently the patients were interviewed regarding each possible adverse effect, utilizing the checklist. A determination was made, between the patient and researcher, as to whether the adverse effect was truly due to the use of the monoclonal. 66% of the patients identified at least one additional adverse effect via the use of a carefully chosen checklist. 18 patients had one additional adverse effect. 56 patients

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identified 2 to 8 additional adverse effects.

An additional line of evidence is the opinion of high prescribers of the drug. This is gleaned from chat boards of headache providers, private correspondence, and discussions during conferences. Some headache providers feel that the CGRP monoclonals are safe and adverse effects are infrequently encountered. Others believe, as I do, that the mAbs result in a number of deleterious effects. There is no consensus at this time.

In addition to headache provider comments, the CGRP patient chat boards provide valuable insight into adverse effects. We assessed 2,800 patient comments regarding adverse effects. We judged 490 to be highly believable. The list of common adverse effects, as identified by the highly believable comments, aligns well with our other lines of evidence.

After assessing the various post-approval lines of evidence, there are signals that the following adverse effects may result from the use of CGRP monoclonals: constipation, anxiety, injection site reactions, weight gain or loss, worsening hypertension, increased headache, insomnia, depression, hair loss, joint pain, fatigue, irritability, muscle pain or cramps, nausea, rash, sexual dysfunction, and tachycardia (or other heart irregularities). Most likely there are others as well. In addition, there have been cases of reversible cerebral vasoconstriction syndrome and stroke. Angina and myocardial infarction have also been reported. Thomas Moore, a leading expert in the acquisition of adverse effects of drugs, published a review of the CGRP monoclonals in the online journal Quarter Watch. Quarter Watch utilizes various resources, including FDA reports and published post-approval studies [5]. The report cites the "sheer number of case reports," and concludes that "… it is likely that adverse effects of this migraine preventive were underestimated in the clinical trials."

This discussion has revolved around short-term adverse effects. Long-term effects, which are unknown at this time, remain a serious concern. CGRP has been important in various species for 400 million years. We ignore evolution at our peril. There are a multitude of beneficial effects partially mediated by CGRP. These include protecting our cardiac and cerebrovascular systems through vasodilatory effects (particularly during stressful conditions), resisting the onset of hypertension, decreasing oxidative stress in the aorta, improving circulation in the face of heart disease(including heart failure), aiding with wound healing, burns, and tissue repair, minimizing the effects of sepsis, aiding in the healing of GI ulcers, protecting the GI mucosa, affecting GI motility, contributing to flushing and thermoregulation, aiding with cold hypersensitivity, regulating bone metabolism, protecting the kidneys in certain pathologic conditions, playing a role in regulating insulin release, affecting metabolism and body weight, and helping to mediate the adrenal glucocorticoid response to acute stress in the mature fetus [6]. The hypothalamic-pituitary-adrenal axis may be affected by CGRP, and this has not been adequately studied. If these mAbs are to be used in adolescents, we must first study the hormonal effects.

The package inserts often do not reflect the reality of the AE profile. I believe that the FDA should overhaul the guidelines as to how adverse events are acquired in formal studies. This situation has been harmful to patients. This is not unique to the mAbs. We should work towards improving the early identification of an accurate adverse effect profile. Certain adverse effects, such as sexual adverse effects, or depression, are missed in formal studies.

The CGRP monoclonal antibodies have been beneficial for many migraineurs. The efficacy of these mAbs rivals that of on a botulinum toxina. However, CGRP plays a crucial role in many physiological processes. There is evidence for a multitude of deleterious effects that result from blocking CGRP. Long-term effects are completely unknown. We should be cautious and judicious in our use of the CGRP monoclonal antibodies.

Disclosure

L. Robbins is a speaker for Abbott Labs, Teva, and Amgen.

References

1. Boldis K, Butala, N (2020) Migraine and CGRP Monoclonal Antibodies: A Review of Cardiovascular Side Effects and Safety Profile. International Journal of Neurology and Neurotherapy 7:101.
2. Robblee J, Devick K, Mendez N, Potter J, Slonaker J, et al. (2020) Real-World Patient Experience with Erenumab for the Preventive Treatment of Migraine. Headache 60: 2014-2025.
3. Alex A, Vaugh C., Rayhill M (2020) Safety and Tolerability of 3 CGRP Monoclonal Antibodies in Practice: A Retrospective Cohort Study. Headache 60: 2454-2462.
4. Robbins L, Phenicie B (2020) CGRP Monoclonal Antibodies for Chronic Migraine Prevention: Evaluation of Adverse Effects Using a Checklist. Practical Pain Management 20: 48-52.
5. Moore T (2019) Aimovig, Ajovy, and Emgality. Quarter Watch Reports 24: 2-4.
6. Robbins L (2018) CGRP Antagonists: Physiologic Effects and Serious Side Effects (Letter). Headache 58: 1469-1471.