

## Migraine Prophylaxis Using Novel Monoclonal Antibody Injections in a Commercial Pilot

Mitchell A. Garber; Joseph I. Sirven; Richard S. Roth; John M. Hemphill

- BACKGROUND:** Frequent migraine headaches are disabling and aeromedically disqualifying. Four new monoclonal antibody medications, targeting calcitonin gene-related peptide (CGRP), have been approved by the U.S. Food and Drug Administration (FDA) since 2018, with more expected in the coming years. These medications present new alternatives for the treatment of migraine unresponsive to other therapeutic and prophylactic agents.
- CASE REPORT:** We present a case of a 45-yr-old commercial pilot who presented with migraine headaches increasing in frequency to 13–15 per month in spite of the use of propranolol for prophylaxis and sumatriptan for abortive treatment of the headaches. Upon presentation, he was not flying due to his frequent headaches and he was started on monthly subcutaneous injections of fremanezumab. Following his second injection, his headaches stopped entirely, and he has continued on the medication and not experienced another migraine headache. He underwent an aeromedical neurology evaluation and consideration for Authorization of Special Issuance of Medical Certificate, which was granted by the Federal Aviation Administration (FAA).
- DISCUSSION:** This is the first case to our knowledge of the successful use of an anti-CGRP monoclonal antibody medication in an active pilot. The pilot appears to be a “super responder” to the medication, having achieved complete remission of a nearly life-long condition. Though only a small portion of treated individuals will see this sort of response, these medications represent an effective additional option for migraine prophylaxis in the pilot population.
- KEYWORDS:** calcitonin gene-related peptide, fremanezumab, migraine headache, pilots.

Garber MA, Sirven JI, Roth RS, Hemphill JM. *Migraine prophylaxis using novel monoclonal antibody injections in a commercial pilot. *Aerosp Med Hum Perform.* 2020; 91(10):824–825.*

The U.S. Federal Aviation Administration (FAA) permits designated Aviation Medical Examiners (AMEs) to issue a medical certificate to pilots with migraine headaches that are mild, occur no more frequently than once a month, and are treated only with a few specific noninjectable, nonnarcotic medications.<sup>2</sup> Medications permitted for prophylaxis of migraine include only calcium channel blockers or beta blockers, assuming no side effects. Otherwise, a history of migraines in a U.S. pilot requires submission of documentation to the FAA for consideration of Special Issuance of Medical Certificate.

A new development in the treatment of migraine headaches has been the discovery of the role played by calcitonin gene-related peptide (CGRP) in migraine symptom expression.<sup>1</sup> CGRP is a trigeminal sensory neuropeptide that has potent and long-lasting vasodilator effects. It has been shown to be selectively released during acute migraine events and such release is prevented by certain drugs used to treat migraine. Monoclonal

antibodies derived from humanized immunoglobulin G have been developed against both CGRP and CGRP receptors; several have shown effectiveness in reducing migraine frequency and are now approved for clinical use. A subset of patients have been identified as “super responders,” achieving complete abolition of migraines on these medications.<sup>4</sup> Until recently, none of the medications targeting CGRP had been approved by the FAA for a pilot to use for the control or prophylaxis of migraine headache.

From Engineering Systems, Inc., Norcross, GA, USA; the Department of Neurology, Mayo Clinic, Jacksonville, FL, USA; Roth Aviation Medical Services, Savannah, GA, USA; and Savannah Neurology Specialists, Savannah, GA, USA.

This manuscript was received for review in June 2020. It was accepted for publication in July 2020.

Address correspondence to: Mitchell A. Garber, M.D., M.P.H., 403 Technology Pkwy, Norcross, GA 30092; magarber@engsys.com.

Reprint & Copyright © by the Aerospace Medical Association, Alexandria, VA.

DOI: <https://doi.org/10.3357/AMHP.5688.2020>

## CASE REPORT

The patient was a 45-yr-old right-handed male commercial pilot. He had a history of migraine headaches since childhood, with a family history of migraines in his brother, sister, mother, and grandmother. He described the headaches as beginning occipitally, developing into a sharp stabbing pain bilaterally, occasionally proceeding to disabling pain in the orbital and nasal areas, predominately on the left side, lasting anywhere from 2 to 6 h, and requiring several hours of bed rest for recovery. He noted associated mild nausea and photophobia, but no vomiting or visual auras. Triggers included chocolate, alcohol, and the odor of certain perfumes.

Previous workup had included complete neurological evaluation, a negative MRI of the brain, and a normal sleep study. He underwent septoplasty which seemed to help with sleep, but which did not affect the headaches. He had previously achieved adequate control of his headaches on propranolol 120 mg/d, prophylactically, and he could get relief with sumatriptan if he used it early enough in the headache. Trials of botulinum toxin injection and occipital nerve blocks did not result in significant reduction in symptom severity or frequency. His frequency and severity of headache increased to the point where he was having 13–15 headaches per month, and he stopped flying altogether.

As he was not flying, his neurologist suggested the use of the new medication fremanezumab, a monoclonal antibody targeting CGRP, which had first been approved for use by the U.S. Food and Drug Administration in September 2018. After his first injection in January 2019, he did not note any significant change. Following the second injection in February 2019, he stated it was as though “a switch had been flipped.” All headaches stopped, and since that time he only reported rare tension headaches, which were successfully managed with acetaminophen. He has continued monthly subcutaneous injections of fremanezumab (225 mg) with no local or systemic side effects.

Evaluation by an FAA consultant neurologist was entirely normal. He had a perfect score (30/30) on the Montreal Cognitive Assessment, and neurological examination findings were completely normal.

FAA policy generally restricts approval of novel medications to those that have been on the market for more than 1 yr. In October of 2019, the pilot requested consideration for Authorization of Special Issuance for his history of migraine headaches controlled with monthly fremanezumab injections and, in December of 2019, authorization was granted. The pilot's authorization was recently extended to 2026, with requirements for twice yearly clinical updates on his condition. This authorization permits the pilot's AME to directly issue his medical certificate following each of his routine medical certification examinations. The pilot is currently regularly flying business jets around the world.

## DISCUSSION

This pilot's headaches fulfilled diagnostic criteria for chronic migraine.<sup>3</sup> Migraine headaches and other chronic headache conditions can adversely affect all aspects of a patient's life, including occupational and aeromedical concerns in the pilot population. The new class of CGRP antagonists present novel options for the treatment and prophylaxis of migraine, and this case demonstrates that, at least in selected cases, these medications may be approved for use by commercial pilots in the United States. Only a minority of patients on such medications will achieve complete migraine remission, but most will see some improvement in headache frequency, which could potentially meet recommended standards for medical certification consideration. Neurological and cognitive effects are not routinely seen or anticipated with these CGRP antagonists; the primary adverse effect reported to be associated with fremanezumab was injection site pain.<sup>5</sup> This favorable side-effect profile suggests that these medications may reasonably be considered for trial use in pilots and others in safety-sensitive positions with inadequately controlled chronic migraine.

## ACKNOWLEDGMENTS

The authors wish to thank the pilot for his kind permission to present his case to the wider aeromedical community.

*Financial Disclosure Statement:* The authors have no competing interests to declare.

*Authors and affiliations:* Mitchell A. Garber, M.D., M.P.H., Engineering Systems, Inc., Norcross, GA, USA; Joseph I. Sirven, M.D., Department of Neurology, Mayo Clinic, Jacksonville, FL, USA; Richard S. Roth, M.D., Roth Aviation Medical Services, Savannah, GA, USA; and John M. Hemphill, M.D., Savannah Neurology Specialists, Savannah, GA, USA.

## REFERENCES

- Edvinsson L. Role of CGRP in migraine. In: Brain S, Geppetti P, editors. Calcitonin gene-related peptide (CGRP) mechanisms. Handbook of experimental pharmacology, vol. 255. Basel, Switzerland: Springer Nature Switzerland AG; 2019:121–130.
- Federal Aviation Administration. 2020 Guide for Aviation Medical Examiners. Washington (DC, USA): Federal Aviation Administration; February 26, 2020.
- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38(1):1–211.
- Israel H, Neeb L, Reuter U. CGRP monoclonal antibodies for the preventative treatment of migraine. Curr Pain Headache Rep. 2018; 22(5):38.
- Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017; 377(22):2113–2122.