Erenumab and Onabotulinumtoxin A Show Additive Effect in Refractory Chronic Migraine

A CASE REPORT

The authors report the case of a patient with refractory CM who showed the greatest improvement with a dual therapy of BTX and the CGRP receptor monoclonal antagonist antibody.

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The prevalence of chronic migraine (CM) is estimated to be about 1.4% to 2.2% worldwide.[1] Several preventive treatments are available for patients afflicted with this condition, including sodium valproate, topiramate, and propranolol. However, many patients do not improve with the traditional preventive therapies and see their quality of life deteriorate. Prophylactic treatment with onabotulinumtoxin A (BTX) injections and, more recently, erenumab (the first calcitonin gene-related peptide receptor that was US FDA-approved for migraine prevention), has showed improvement in the management of patients with refractory chronic migraine.[2,3]

Unfortunately, approximately 50% to 60% of patients with CM do not show improvement with either BTX (24 weeks) or erenumab (12 weeks).[2-5] Herein, the authors report the case of a patient with refractory CM who showed the greatest improvement with a dual therapy of BTX and erenumab.

Case Presentation

History

A 52-year-old woman afflicted with refractory CM for more than 10 years presented to the clinic. She had not worked in 3 years. In 2017, brain MRI revealed several non-specific T2/FLAIR anomalies, most likely due to her migraine attacks. This patient had trialed several classical preventive treatments, including amytriptyline and propranolol. She was also treated with duloxetine, candesartan, and verapamil. She presented to the clinic using rizatriptan, dimenhydrinate, and fiorinal-C1/4, as well as meperidine for acute migraine management, and prescribed cannabi-

Table I: Monthly Medication Usage by Case Patient.

	Before treatment	BTX	BTX and Erenumab	Erenumab	Erenumab and BTX
Rizatriptan (10 mg)	9.8	6.3	4.7	9	1.5
Fiorinal C1/4*	2.9	2.5	2.2	8	1.2
Dimenhydrinate (50 mg)	6.7	5	4.2	14	3.6
Meperidine (100 mg)	10	7.5	5.8	14	3.6
Acetaminophen (500 mg)	67	42	33	110	30
Medical cannabinoids (days)	8.3	6.7	2.4	10	1.8

L to R: chronological medication usage by the case patient before onabotulinumtoxin A (BTX) or erenumab treatment, with BTX alone, BTX and erenumab, eenumab alone after stopping BTX and, finally, with restitution of erenumab and BTX. The quantity of each medication used monthly is indicated, except for medical cannabinoids where the number of daily usages per month is noted.
*Fiorinal C1/4 contains 330 mg aspirin, 40 mg caffeine, 15 mg codeine, and 50 mg butalbital.

noids (without THC) (see Table I for doses). None of these treatments significantly improved her pain and, thus, her quality of life was reduced. She reported visiting her local emergency room (ER) three to four times per month for acute management despite her medications.

Treatment Course: From BTX to Erenumab to Dual Therapy

In November 2017, a treatment with BTX was given to the patient (standard injection protocol performed every three months). At 1-year follow-up, she reported that her ER visits had reduced to about one per month in 2018 (see Tables I and II). The severity of her acute migraine episodes was also reduced. She was using less abortive medications and reported an approximate 30% reduction in monthly migraine days (27 to 18). While BTX improved her condition, her quality of life was still hindered by the frequency of her monthly migraine days and the need of medical cannabinoids and other abortive medications.

In December 2018, she received her first monthly erenumab injection (140 mg). At 3-month follow-up, the frequency of her migraine days further decreased. The patient reported no ER visits in 3 months and her abortive medication intake further decreased by 20% to 40%. Interestingly, her over-the-counter abortive medications showed an increased efficacy. See Tables I and II.

Assuming erenumab would be a sufficient treatment, the patient's BTX treatment was aborted following her last CGRP receptor inhibitor injection in February 2019. She unfortunately had a surge of migraine days (from 10 to 15) and visited the ER four times during April and May 2019. The severity of her migraine episodes and her abortive treatment intake increased significantly during that time as well.

Thus, the patient's BTX treatment was resumed in June 2019 and she continued her erenumab monthly injections. Between July and September 2019, she reported 3 migraine attacks and no ER visits. Her abortive medication intake decreased significantly. The patient showed the greatest improvement in her quality of life while being treated with both erenumab and BTX together. She has since been able to resume work while on the ongoing dual therapy.

Discussion

The socio-economic burden of chronic migraine on patients and their quality of life is well established. The impact can be significant enough to deter their professional careers.[6] Medical resource usage, such as ER visits, may be prevalent in patients with uncontrolled CM, which can contribute to the societal burden caused by this disease.[1,7,8] Although several treatments are available to prevent debilitating migraine attacks, there is still an estimated 3% of patients who progress from an episodic to the chronic form of the disease.[9,10]

Preventive treatments using either onabotulinumtoxin A and erenumab showed promising results in patients who had previously failed on at least two different preventive medications.[2-5,11] More importantly, recent studies have demonstrated safety and efficacy in using the new CGRP preventive class, including erenumab.[12,13] To the authors' knowledge, this is the first case report of a patient with refractory CM who improved utilizing dual therapy.

It is hypothesized that the antagonistic effect of erenumab on the peripheral CGRP receptor acts on smooth muscle cells within meningeal vessels to decrease inflammation and prevent vasodilation. The meningeal vessels are innervated by small afferent nerves to the trigeminal ganglion (TG) and ultimately to the trigeminal nucleus caudalis (TNC), which can be activated by several pro-inflammatory substances including histamines, prostaglandins, nitric oxide, and tumor necrosis factor.

Table II: Monthly Migraine Days and Emergency Room Visits by Case Patient.

	Before treatment	BTX	BTX and Erenumab	Erenumab	Erenumab and BTX
Migraine days	27	18	10	15	1
Emergency room visits (days)	3 to 4	1	0	2	0

L to R: chronological migraine days and emergency room visits before onabotulinumtoxin A (BTX) or erenumab treatment, with BTX alone, BTX and erenumab, erenumab alone after stopping BTX, and finally, with restitution of erenumab and BTX.

While the CGRP receptor is also present on the TG, thalamus, hypothalamus, brain stem, and cortex, antibodies do not cross the blood-brain barrier to act upon them.[14] Fortunately, it is hypothesized that local sensory and motor terminals can take up and carry the BTX to central terminals. This axonal transport causes SNARE protein cleavage in dorsal root ganglion, TG, and TNC where it reduces the release of CGRP.[15] Thus, in theory, these two mechanisms seem to be complementary. Erenumab may act in the periphery by attenuating the effect of circulating CGRP ligands, while BTX may act upstream by inhibiting the release of the ligand.

Erenumab treatment, thus, may be a beneficial option for patients with CM showing limited benefit with BTX treatment. In support of this hypothesis, two patients in our erenumab-treatment cohort (unpublished data) showed great improvement with erenumab alone after a failure with BTX therapy alone (over 75% decrease in their migraine days at 3 months). Thus, a failure with one of these two treatments does not preclude a good outcome with the other one.

Of note, erenumab was the only approved CGRP receptor inhibitor approved in the authors' location at the time of this case. Other medications in the class approved since then act by antagonizing the ligand and not the receptor; this distinct mechanism makes it unclear whether a similar outcome would be achieved with dual therapy with another CGRP receptor inhibitor and BTX.

Conclusion

The authors present what they believe is to be the first case report suggesting an additive effect of onabotulinumtoxin A and erenumab treatment in a patient with refractory chronic migraine. We hypothesized that the putative central effect of BTX, which reduces the release of CGRP, and the antagonistic effect of erenumab on peripheral CGRP receptors may result in an additive response in patients with refractory CM. This dual therapy should be considered when a patient fails to respond to classical prophylactic treatment and to either BTX or erenumab therapy alone. The quality of life of the patient may improve greatly while the consumption of migraine-abortive medications (and their side effects) is significantly reduced. This report may provide evidence that could encourage insurance providers to cover the cost of both BTX and erenumab in patients with refractory chronic migraine. •

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