Neurological Sciences (2021) 42:5373–5376
https://doi.org/10.1007/s10072-021-05547-x

BRIEF COMMUNICATION

Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series

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Received: 13 April 2021 / Accepted: 31 July 2021 / Published online: 18 August 2021

Abstract

Aims Clinical trials for calcitonin gene-related peptide (CGRP) inhibitors excluded the concomitant use of onabotulinumtoxinA; thus, there is a lack of efficacy and safety data of the combined therapies. Our study aims to examine the effectiveness of CGRP inhibitors with onabotulinumtoxinA by evaluating migraine reductions in headache days and severity.

Methods Seventeen patients with chronic migraines were identified who had a partial or poor response to onabotulinumtoxinA, and were placed on dual therapy with a CGRP inhibitor. Patients' initial headache days and severity ratings were compared to final values taken 1–6 months after adding the CGRP inhibitor to their treatment regime. Comparisons between headache days and severity ratings prior to and during dual treatment were performed utilizing the Kruskal–Wallis test. The significance was set at $p < 0.05$.

Results Of 17 patients (16F/1 M), $n = 9$ were taking fremanezumab, $n = 4$ were taking erenumab, and $n = 4$ were taking galcanezumab. Patients' average headache days per month was reduced from 27.6 ± 4.8 initially to 18.6 ± 9.4 post-treatment ($p = 0.00651$), and their average pain level was reduced from 8.4 ± 1.4 out of 10 to 5.4 ± 2.5 ($p = 0.00074$). No serious adverse side effects were reported from patients on dual therapy.

Conclusion Patients with suboptimal response to onabotulinumtoxinA may benefit from CGRP inhibitors' addition to their migraine regimens. Placebo-controlled randomized studies are advised to corroborate this finding.

Keywords Chronic migraine · Anti-CGRP mAb · Fremanezumab · Erenumab · Galcanezumab

Introduction

Two preventative treatments for migraines include the relatively recently approved CGRP inhibitors and onabotulinumtoxinA [1]. The four FDA-approved anti-CGRP mAbs are erenumab, galcanezumab, fremanezumab, and eptinezumab [2], and the two FDA-approved gepants are ubrogepant and rimegepant [3]. A pooled analysis suggested that the four approved anti-CGRP mAbs have a weighted average of 1.44 fewer monthly migraine days and 1.28 fewer acute monthly migraine-specific medication days in patients compared to the placebo [4]. Clinical trials on ubrogepant and rimegepant for acute migraine treatment found pain freedom occurred at 2 h in 20.5% of patients compared to placebo of 11.45%. Rimegepant, the only gepant used also as a preventative treatment, achieved 6.4 fewer monthly migraine days in chronic migraine patients [3]. OnabulinumtoxinA is 51% effective in eliciting a complete response to treatment and 28% effective in eliciting a partial response [5]. However, CGRP inhibitors and onabotulinumtoxinA have not been clinically tested in combination for migraine prevention. Therefore, it is unclear whether the coupled therapy yields a synergistic effect and any clinically significant safety concerns. Herein, we report our clinical experience in the dual use of onabotulinumtoxinA and CGRP inhibitors in patients with chronic migraine.

Methods

Between May 2018 to June 2020, 17 cases of chronic migraine with suboptimal response to onabotulinumtoxinA injections were gathered for which a CGRP inhibitor

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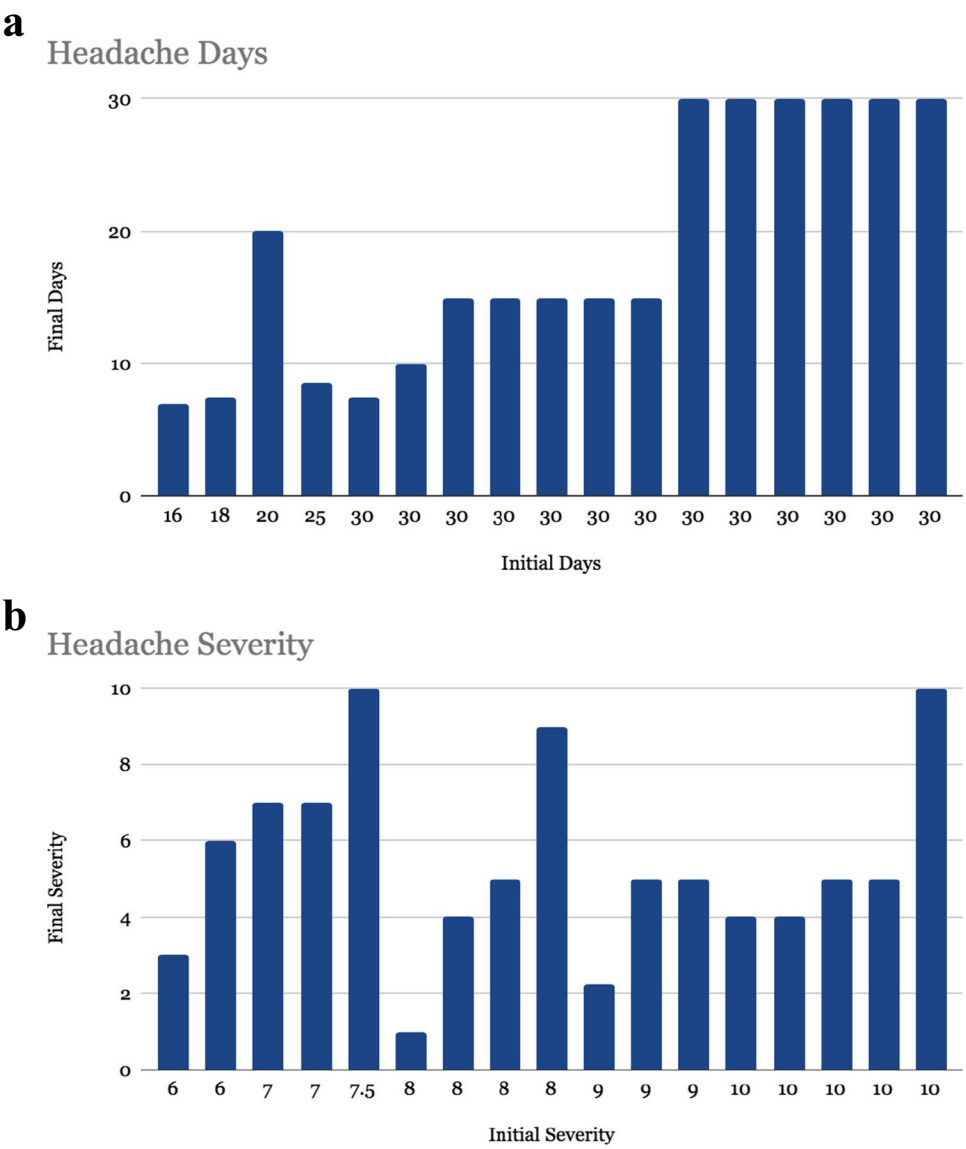

Fig. 1 Initial headache days per month patients experienced during onabotulinumtoxinA monotherapy versus final headache days per month patients experienced 1–6 months after adding a CGRP inhibitor to their treatment regime **(a)**. Initial headache severity patients experienced during onabotulinumtoxinA mono-therapy versus final headache severity patients experienced 1–6 months after adding a CGRP inhibitor to their treatment regime **(b)**

was added to their migraine prevention drug regimen. The CGRP inhibitors prescribed were all within the anti-CGRP monoclonal antibodies (mAbs) class: fremanezumab, erenumab, and galcanezumab. No patient was placed on dual therapy with a gepant (ubrogepant, rimegepant), as these two drugs, along with the anti-CGRP mAb, eptinezumab, were the most recent approvals within the class of CGRP inhibitors. Variables were recorded for the age of onset, current age, gender, and conditions commonly associated with migraines (anxiety, depression, and sleep disorders). Reductions in migraine burden were assessed by examining changes in headache days and severity.

Pre- and post-dual onabotulinumtoxinA and CGRP-inhibitor therapy headache days and severity were evaluated over 1–6 months. Headache severity was determined on a clinical impression 0 to 10 pain scale. Severity ratings were cross-referenced with an independent review of patient medical records based on the pain description, adverse events experienced, pain medication pattern of use, and the degree to which headaches interfered with daily life. Comparisons between headache days and severity ratings prior to and during dual treatment were performed utilizing the Kruskal–Wallis test. The significance was set at $p < 0.05$.

Results

Of the 17 patients (female $n = 16$, male $n = 1$), the current ages ranged from 20 to 73, with a median age of 46.5 years old. The age of migraine onset ranged from 4

Table 1 Patients' response to migraine dual therapy 1–6 months after the addition of a CGRP inhibitor with onabotulinumtoxinA injections

Characteristics	Number of Patients									
	Basic response to dual therapy				Percent reduction to dual therapy					
	Increased	Unchanged	Decreased	P-value	− 50 to − 25%	− 25–0%	0–25%	25–50%	50–75%	75–100%
Headache days	0	7	10	0.00651	0	0	7	0	9	1
Headache severity	2	4	11	0.00074	1	1	4	3	6	2
	Pre-dual therapy group						Post-dual therapy group			
	Minimum	Maximum	Median	Average ± standard deviation			Minimum	Maximum	Median	Average ± standard deviation
Headache days	16	30	30	27.6 ± 4.8			7	30	15	18.6 ± 9.4
Headache severity	6	10	8	8.4 ± 1.4			1	10	5	5.4 ± 2.5

to 59, with a median age of 18.3 years. Interestingly, eight patients reported childhood-onset (≤ 18 years), and eight patients reported adult-onset (> 18 years). One patient did not report their age of onset. Of the common coexisting migraine conditions evaluated, 4 patients suffered anxiety, 4 patients suffered depression, and 6 patients suffered sleep disorders (bruxism $n = 1$, hypersomnia $n = 1$, insomnia $n = 4$). Nine patients were taking fremanezumab, 4 patients were taking erenumab, and 4 patients were taking galcanezumab.

All patients were initially being treated with onabotulinumtoxinA injections, then given an anti-CGRP mAb as combined therapy with onabotulinumtoxinA for further migraine prevention. Patients experienced initial headache days per month of [16, 30, 30, 27.6 ± 4.8] ([min, max, median, avg ± std]), and final headache days of [7, 30, 15, 18.6 ± 9.4]. Ten patients experienced reductions in headache days, and 7 patients experienced no reduction. Patients experienced initial headache severity ratings of [6, 10, 8, 8.4 ± 1.4], and final severity ratings of [1, 10, 5, 5.4 ± 2.5]. Eleven patients improved, 4 patients experienced no change, and 2 patients worsened in headache severity (Fig. 1, Table 1). A mean improvement of + 12.6 headache-free days was observed in fremanezumab patients, + 6.4 in erenumab patients, and + 3.8 in galcanezumab patients. The Kruskal–Wallis rank-sum test for headache days yielded statistical significance with a H statistic value of 7.4041 (1, $N = 34$) and a p-value of 0.00651. For headache severity, the H statistic value was calculated at 11.3938 (1, $N = 34$) with a p-value of 0.00074.

No serious adverse side effects from dual therapy were reported. Some patients experienced mild reactions of irritation at the injection site and constipation, which are known side effects of anti-CGRP mAbs [2].

Discussion

A substantial portion of patients experienced meaningful reductions in both headache days and severity. The response rate to dual treatment was 58.82% in headache days and 64.71% in headache severity. Moreover, the addition of an anti-CGRP mAb with onabotulinumtoxinA injections reduced the onset of migraines and/or the discomfort of developing migraines. Additionally, the combined treatment was observed to be clinically safe in patients. These findings suggest that patients who suffer from severe, intractable migraines may benefit from onabotulinumtoxinA and anti-CGRP mAb dual therapy. A possible synergistic mechanism for the dual therapy might be operating at both the receptor and ligand level, which lowers CGRP levels and correlates with lower migraine pain severity [6].

Our dual therapy case series aligns with the recently published similar case series from Talbot and colleagues [7] that evaluated dual therapy with erenumab and onabotulinumtoxinA. Their patients experienced a mean improvement of + 6.9 headache-free days 6 months after adding erenumab to their treatment regime, while our patients experienced a mean improvement of + 9.0 after 1–6 months. Additionally, their patients reported using less analgesia and triptan overuse suggesting a decline in headache severity consistent with our results. Both studies observed a favorable response to combined treatment with a CGRP inhibitor and onabotulinumtoxinA; however, their results are based on observations with erenumab and our results include data from fremanezumab and galcanezumab in addition to erenumab [7].

Since anti-CGRP mAbs were recently approved (May 2018 first approval, Feb 2020 last two approvals) [3], longitudinal data was limited, and only short-term effectiveness (1–6 months) could be examined. Additionally, only a modest sample size was being treated with the combined therapy. Nonetheless, our 17 patient cohort proposed that additional therapeutic effect could be gained by adding a CGRP inhibitor to chronic migraine patients who experienced a partial response to onabotulinumtoxinA injections.

Conclusion

Our case series suggests that a clinically relevant portion of onabotulinumtoxinA partial responders may obtain incremental headache relief by adding a CGRP inhibitor without compromising the safety and tolerability of their drug regimen. Future placebo-controlled, randomized studies are required to confirm these observations.

Acknowledgements The authors wish to thank the staff at Hawaii Pacific Neuroscience for their valuable assistance in gathering the data.

Author contribution All authors contributed to the conception of the work, analysis and interpretation of the data. TT and EC drafted the letter, and RT, BN, YL, JL, VV, JV and KKL revised it critically for intellectual content.

Data availability Deidentified data can be made available upon request.

Declarations

Ethics approval and consent Patients' records confidentiality was maintained and data deidentified. Written informed consent was not obtained, as this Letter to the Editor is based on the authors' clinical experience.

Consent for publication All authors give consent for publication of this Letter to the Editor.

Conflict of interest The authors declare no competing interests.

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