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ORIGINAL RESEARCH ARTICLE

Synergism of Anti-CGRP Monoclonal Antibodies and OnabotulinumtoxinA in the Treatment of Chronic Migraine: A Real-World Retrospective Chart Review

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Abstract

Background Many patients with chronic migraine do not achieve clinically meaningful improvement in their headache frequency with monotherapy. The burden associated with chronic migraine calls for a multifaceted treatment approach targeting multiple aspects of migraine pathophysiology.

Objective The aim of this study was to evaluate the effect of concurrent anti-calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb) and onabotulinumtoxinA (onabot) treatment on median monthly migraine days (MMD) in patients with chronic migraine, through a retrospective study.

Methods The electronic medical records of Cleveland Clinic patients either concurrently (dual therapy) or consecutively (monotherapy) treated with anti-CGRP mAbs and onabot between June 2018 and November 2021 were extracted. Only adult patients (≥ 18 years of age) were included in this study. MMDs for 194 concurrently treated (86.6% female and a median [interquartile range] age of 51 [41–61] years) and 229 consecutively treated (88.2% female and median age of 47 [IQR 39–57] years) patients were examined at baseline, after first therapy of either anti-CGRP mAb or onabot, and following dual therapy for 3 consecutive months. The reduction of MMDs for each treatment group were compared. The same approach was utilized to compare consecutive monotherapy at separate times ($n = 229$) and dual-therapy groups.

Results The initial treatment of the dual-therapy group reduced the median (IQR) MMDs from 30 (30–30) to 15 (12–30) [$p < 0.0001$]. After initiation of dual therapy, the median MMDs was further decreased from 15 (12–30) to 8 (3–22) [$p < 0.0001$]. A majority [132/194 (68.0%)] of the dual-therapy patients reported a ≥ 50% reduction in MMD and 90/194 (46.4%) reported a ≥ 75% reduction. For the consecutive monotherapy group, median MMDs changed from a baseline of 30 (25–30) to 15 (8–25) from onabot monotherapy and decreased from 25 (15–30) to 12 (4–25) after anti-CGRP mAb monotherapy. Almost half (113/229 [49.3%] from onabot, and 104/229 [45.4%] from anti-CGRP mAb) of these patients achieved a ≥ 50% reduction in MMDs and a minority (38/229 [16.6%] from onabot, and 45/229 [19.7%] from anti-CGRP mAb) achieved a reduction of ≥ 75%. Additionally, dual therapy showed significant improvement in MMDs compared with monotherapy of either treatment ($p < 0.0001$).

Conclusion Dual therapy of anti-CGRP mAbs and onabot may be more efficacious than monotherapy, possibly due to their synergistic mechanisms of action.

Amira Salim and Elise Hennessy were co-first authors on this work.

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Key Points

The baseline migraine days per month decreased after initiation of the first therapy (anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies or onabotulinumtoxinA), and led to a further decrease in migraine days with the addition of the second therapy.

The migraine days before treatment had a median (interquartile range) of 30 (30–30) days per month, which decreased to 15 (12–30) migraine days after the first therapy and fell to 8 (3–22) migraine days after dual therapy. However, monotherapy of onabotulinumtoxinA changed from 30 (25–30) to 15 (8–25) monthly migraine days, and the migraine days per month decreased from 25 (15–30) to 12 (4–25) with anti-CGRP monoclonal antibody monotherapy.

Combined treatment of anti-CGRP monoclonal antibodies and onabotulinumtoxinA were more beneficial than monotherapy alone when examining the total reduction in monthly migraine days.

1 Introduction

Migraine is the second most disabling condition worldwide and affects approximately 12% of the population [1, 2]. Chronic migraine is associated with impairment in quality of life, increased medical and psychiatric comorbidities, and accounts for significant health resource utilization [1–3]. Many patients with chronic migraine do not achieve clinically meaningful improvement in their headache frequency and intensity with monotherapy [4]. Therefore, the immense burden associated with chronic migraine calls for a multifaceted treatment approach targeting multiple aspects of migraine pathophysiology in an effort to improve patient outcomes.

The first class of preventive medications specific to migraine pathophysiology, the anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs), gained US FDA approval in 2018 [5, 6]. Since the first anti-CGRP mAb was approved, the number has increased to four in total: erenumab, fremanezumab, galcanezumab, and eptinezumab [5–11]. The European Headache Federation (EHF) found sufficient evidence to recommend the four anti-CGRP mAbs for the treatment of episodic and chronic migraine. Additionally, they suggest anti-CGRP mAbs be a first-line treatment option for individuals who require preventative care [12]. CGRP is a 37 amino acid peptide that has a critical role in migraine pathophysiology [13]. CGRP receptors are present throughout regions involved in migraine pathogenesis, including the meningeal vasculature, trigeminal ganglia, and other numerous sites throughout the peripheral and central nervous system [13, 14]. CGRP is released from trigeminal axons onto meningeal blood vessels, causing vasodilation and activation of trigeminal neurons. CGRP is released in the trigeminal ganglion by C-fibers and binds to receptors on Aδ-fibers and glial cells facilitating trigeminal nociceptive transmission and triggering proposed neurogenic inflammation [13]. CGRP levels have been demonstrated to rise during migraine attacks and fall interictally as well as after abortive treatment [15–17]. Patients with migraine have higher levels of serum CGRP than controls, and infusion of CGRP precipitates migraine-like headaches [17, 18].

OnabotulinumtoxinA (onabot) was first demonstrated to have an effect on migraine when being used in patients for hyperfunctional lines of the face [19]. This finding led to the first open-label, non-randomized study in 2000 [20]. Onabot gained FDA approval for chronic migraine in 2010 after the PREEMPT trials showed significant reduction in headache days [21, 22]. The EHF recommends onabot as a preventative treatment option for chronic migraine [23]. Onabot acts by cleaving soluble N-ethylmaleimide-sensitive fusion attachment protein (SNAP-25), an essential protein for soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE)-mediated vesicle trafficking [23–27]. Vesicle fusion with the inner synaptic membrane inhibited by onabot impacts migraine pathology by preventing the exocytosis of excitatory and pro-inflammatory neurotransmitters, such as CGRP, glutamate, and substance P. Additionally, this inhibits the insertion of the peripheral receptors (e.g. transient receptor potential cation channel subfamily V member 1 [TRPV1]), into the synaptic membrane, which are vital for pain signaling [27].

Onabot has been demonstrated to selectively inhibit unmyelinated C-fibers but not Aδ-meningeal nociceptors [28–30]. The anti-CGRP mAbs that target the CGRP peptide have been shown to prevent the activation of Aδ-fibers but not C-fibers [31]. Therefore, concurrent use of anti-CGRP mAbs with onabot may have a synergistic effect with targeting both Aδ-fibers and C-fibers. Previous studies have demonstrated that anti-CGRP mAbs and onabot may be efficacious in combination for the treatment of migraine [32–35]. We hypothesize that the possible synergistic mechanisms of onabot and anti-CGRP mAbs will result in improved treatment outcomes and reduced migraine frequency for patients with chronic migraine when compared with monotherapy.

2 Methods

All patients included in this study received a diagnosis, had appointment notes written, and had drugs prescribed by the United Council for Neurologic Subspecialties (UCNS) board-certified headache providers at the Cleveland Clinic. The patients' self-reported MMD data were extracted from templated Epic appointment notes that were recorded by their providers. Thus, there is consistency in data reported despite a variety of different headache providers treating the patients.

2.1 Dual-Therapy Dataset

Inclusion in the dual-therapy dataset required patients be at least 18 years of age, have an official migraine diagnosis, completed a minimum of 3 consecutive months of concurrent anti-CGRP mAbs and onabot injections (between June 2018 and November 2021), and had their monthly migraine days (MMDs) recorded at baseline, after the first therapy and after dual therapy. Although the inclusion criteria include any migraine diagnosis, in order to qualify for these preventative treatments in general and receive dual therapy, the patients have likely not responded to multiple previous medications and have chronic migraine. The inclusion criteria were confirmed with a thorough chart review for each patient; 194 individuals met the study criteria and were included in the final dual-therapy group (Fig. 1). In addition to MMDs, clinical data such as the specific anti-CGRP mAbs prescribed, length of time on first therapy before dual therapy was initiated, early onabot wearing off, and migraine diagnosis (with or without aura) were extracted from the EPIC systems. Demographic data, including sex, age, and race, were gathered from EPIC for the entire sample.

2.2 Dual-Therapy Analysis

The dual-therapy dataset consisted of 194 patients with concurrent onabot and anti-CGRP mAb therapies. Additionally, to determine if the order of therapies impacts response outcomes, the dataset was separated into patients started on onabot first before dual therapy ($n=171$) and patients with anti-CGRP mAb treatment before dual therapy ($n=23$). The sample size was based on the available data. No imputation was conducted for the dual-therapy group as there were no missing data for all variables extracted and evaluated. The primary analysis of these data compared the MMDs for the dual-therapy dataset among three time points: baseline, after first therapy, and after dual therapy. This same analysis was repeated separately for the onabot-first and the anti-CGRP mAb-first sub-datasets. A non-parametric test was determined most fitting for the data. A comparison of the three treatment time points was done using the Friedman test. To better understand which specific treatment time point

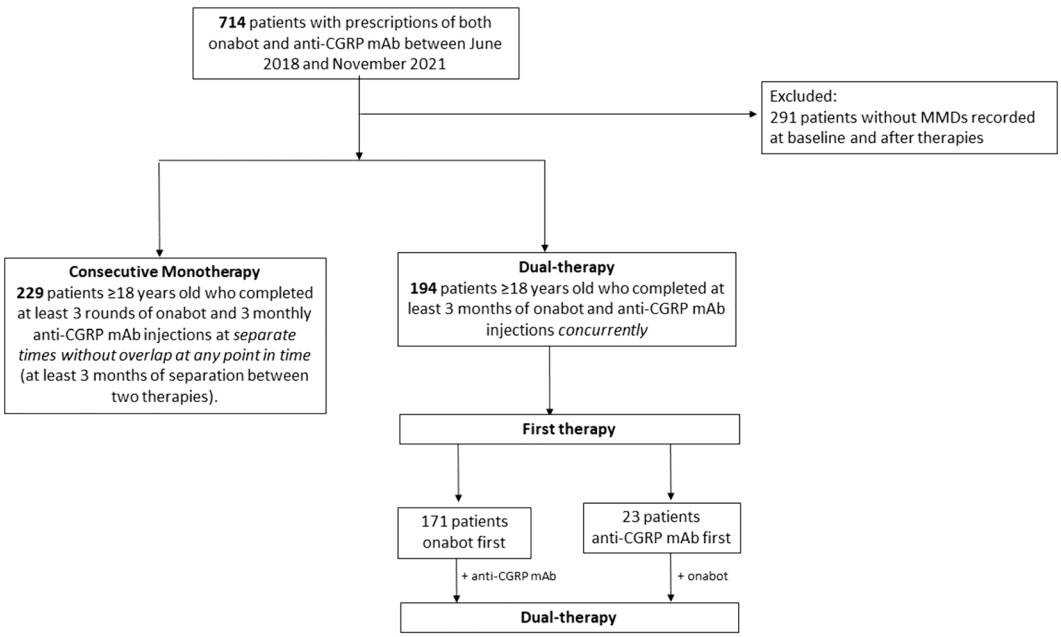

Fig. 1 Description of dataset analyzed. The first analysis was completed among the dual-therapy group. An additional analysis compared a separate consecutive monotherapy group with the dual-therapy dataset. *Anti-CGRP mAb* anti-calcitonin gene-related peptide monoclonal antibodies, *MMDs* monthly migraine days, *onabot* onabotulinumtoxinA

differed from the others, the Dunn's multiple comparison test was employed. We did not correct for multiple comparisons due to the exploratory nature of this study and therefore potential interesting findings were not missed. Additionally, the 'reduction of MMDs' or the difference of MMDs from baseline to the first therapy, was compared with the reduction of MMD after combined treatment with the Wilcoxon matched-pairs signed-rank test.

2.3 Consecutive Monotherapy Dataset

To further examine the impact of dual therapy, we identified a consecutive monotherapy group (individuals who received anti-CGRP mAbs and onabot separately) to serve as a comparator. The decision to use consecutive monotherapy patients as a comparison group was made to avoid individual differences in treatment response on a single treatment, and to ensure that all patients in the comparison group were good candidates for both onabot and anti-CGRP mAbs.

For the consecutive monotherapy group, the inclusion criteria were age ≥ 18 years, baseline and after treatment MMDs recorded, and treated with a minimum of three rounds of onabot and three monthly anti-CGRP mAb injections at separate times with no overlap. The exclusion criteria were concurrent treatment at any point in time and we required at least 3 months of separation after the last therapy (onabot or anti-CGRP mAb) before the next therapy was started, to limit any possible effect of the previous treatment. Each patient was confirmed to meet the inclusion criteria with a chart review; 229 patients were included in the consecutive monotherapy sample (Fig. 1).

2.4 Comparison of Consecutive Monotherapy and Dual Therapy

Similar to the dual-therapy dataset, consecutive monotherapy patients had no missing data for the variables extracted. Improvement was assessed through the reduction in MMD. The Kruskal–Wallis test compared MMD reductions among consecutive monotherapy patients while receiving onabot monotherapy, consecutive monotherapy patients while receiving anti-CGRP mAb monotherapy, and dual-therapy patients. Dunn's multiple comparison test was used post hoc for pairwise comparisons. Lastly, to compare the reduction in MMDs between the dual-therapy group and the consecutive monotherapy group (MMD reduction following both consecutive monotherapies), a Mann–Whitney *U* test was used.

For all tests, a two-tailed *p*-value < 0.05 indicated significant differences. Unless noted otherwise, the median and interquartile ranges were used to report all study variables due to the non-parametric nature of the data. The 95% confidence intervals (CIs) were also reported. No statistical power calculation was conducted prior to the study. The Kruskal–Wallis, Dunn's comparison, and Mann–Whitney *U* (two-tailed) tests were completed in GraphPad Prism version 9.4.0 (GraphPad Software, Inc., San Diego, CA, USA).

3 Results

3.1 Dual-Therapy Dataset

A retrospective review of Cleveland Clinic patients with prescriptions of both anti-CGRP mAb and onabot between June 2018 and November 2021 was completed for this study (Fig. 1). A total of 714 patients had an onabot and anti-CGRP mAb prescription within the time frame. This patient list was then separated into the dual-therapy ($n = 194$) and consecutive monotherapy ($n = 229$) datasets based on their specific inclusion criteria. Overall, 291 patients did not meet the criteria for either therapy group.

Demographic and clinical characteristics are summarized in Table 1. Among these patients, the median age was 51 (41–61) years and a majority of the patients were women (86.6%). With regard to migraine type, 164 (84.5%) patients experienced migraine without aura and 30 (15.5%) experienced migraine with aura. Regarding specific anti-CGRP treatment, 58.8% of patients were taking erenumab, 22.2% of patients were taking galcanezumab, and 19.1% of patients were taking fremanezumab. None of the patients in our dataset received eptinezumab. The majority of patients received dual therapy for > 6 months (81.4% [158/194]). The early diminishment in efficacy for onabot is a noted occurrence and a reason why dual therapy may be a beneficial approach for some patients. A total of 50.5% (98/194) of patients experienced wearing off from onabot. The wear-off occurred a median of 2 (2–4) weeks before the next cycle of injections.

3.2 Dual-Therapy Analysis

Patients were receiving their first therapy (with either onabot or anti-CGRP mAb) for a median of 1 (0.5–1.7) year prior to initiation of dual therapy (Table 1). When comparing MMDs at baseline to after first therapy with dual therapy, regardless of which therapy was used first, the first therapy reduced the median MMDs from 30 (30–30) to 15 (12–30) (Table 2). After initiation of dual therapy, the MMDs was further decreased to 8 (3–22). The reduction of MMDs was significant when comparing the first therapy and dual therapy ($p < 0.0001$) (Table 3, Fig. 2c). From baseline to following dual therapy, 132/194 (68.0%) patients reported a ≥ 50% reduction in MMD and 90/194 (46.4%) reported a ≥ 75% reduction (Table 2).

Table 1 Characterization of dual-therapy dataset at baseline

Demographic variables	Onabot first	CGRP mAb first	Full cohort
Total, *n*	171	23	194
Sex			
Female	150 (87.7)	18 (78.3)	168 (86.6)
Male	21 (12.3)	5 (21.7)	26 (13.4)
Age, years [median (Q1–Q3)]	53 (42–61)	40 (28–50)	51 (41–61)
Racial background			
American Indian/Alaska Native	1 (0.6)	–	1 (0.5)
Asian	1 (0.6)	–	1 (0.5)
Black	12 (7.0)	–	12 (6.2)
Multiracial/multicultural	3 (1.8)	–	3 (1.5)
White	150 (87.7)	21 (91.3)	171 (88.1)
Other	4 (2.3)	2 (8.7)	6 (3.1)
Migraine type			
Migraine without aura	149 (87.1)	15 (65.2)	164 (84.5)
Migraine with aura	22 (12.9)	8 (34.8)	30 (15.5)
Anti-CGRP mAbs			
Erenumab (FDA approval: 17 May 2018)	104 (60.8)	10 (43.5)	114 (58.8)
Galcanezumab (FDA approval: 27 September 2018)	38 (22.2)	5 (21.7)	43 (22.2)
Fremanezumab (FDA approval: 14 September 2018)	29 (17.0)	8 (34.8)	37 (19.1)
Eptinezumab (FDA approval: 21 February 2020)	0 (0)	0 (0)	0 (0)
Treatment			
First therapy, years [median (Q1–Q3)]	1 (0.8–2.0)	0.4 (0.3–0.5)	1 (0.5–1.7)
Onabot wear-off, weeks [median (Q1–Q3)]	2 (2–4)	2 (2–2)	2 (2–4)
Onabot wear-off	92 (53.8)	6 (26.1)	98 (50.5)
3–5 months of dual therapy	31 (18.1)	5 (21.7)	36 (18.6)
> 6 months of dual therapy	140 (81.9)	18 (78.3)	158 (81.4)

Data are expressed as *n* (%) unless otherwise specified

Onabot onabotulinumtoxinA, *anti-CGRP mAbs* anti-calcitonin gene-related peptide monoclonal antibodies, *Q1–Q3* quarter 1–quarter 3 (interquartile range), *Onabot first* dual-therapy patients who received onabotulinumtoxinA first before adding anti-CGRP monoclonal antibodies, *CGRP mAb first* dual-therapy patients who received anti-CGRP monoclonal antibodies first before adding onabotulinumtoxinA

The majority of patients were receiving onabot first (88.1% [171/194]) and were receiving treatment for 1 (0.8–2.0) year prior to the initiation of concurrent anti-CGRP mAb dual therapy (Table 1). Onabot therapy-first reduced the MMDs from a median of 30 (30–30) to 19 (12–30) days (Table 2). After the addition of an anti-CGRP mAb to onabot, the median MMDs was further decreased from 19 (12–30) to 12 (3–20). The reduction was significant when comparing onabot therapy and dual therapy ($p < 0.0001$) (Table 3, Fig. 2a). From baseline to following dual therapy, 118/171 (69.0%) patients reported a ≥ 50% reduction in MMDs and 80/171 (46.8%) reported a ≥75% reduction (Table 2).

The 23 patients who were started on an anti-CGRP mAb first (11.9% [23/194]) were receiving treatment for an average of 0.4 (0.3–0.5) years prior to initiation of dual therapy (Table 1). Anti-CGRP mAb therapy reduced the median MMDs from 30 (20–30) to 15 (15–30) (Table 2). After the addition of onabot to the anti-CGRP mAb, the MMDs was further decreased from a median of 15 (15–30) to 7 (3–28). No significant difference was found between MMD at baseline and after anti-CGRP mAb first ($p = 0.122$), but this may be from the lack of power from the small sample size. However, there was a significant difference when comparing baseline MMD with dual therapy, and anti-CGRP mAb initial treatment with dual therapy ($p < 0.0001$ and $p = 0.008$, respectively) (Table 3, Fig. 2b). From baseline to following dual therapy, 14/23 (60.9%) patients reported a ≥ 50% reduction in MMD and 10/23 (43.5%) reported a ≥ 75% reduction (Table 2).

3.3 Consecutive Monotherapy Dataset

Overall, 229 patients met the criteria of consecutive monotherapy from the 714 patients with prescriptions of both onabot and anti-CGRP mAb (Fig. 1). The characteristics

Table 2 Evaluation of monthly migraine days for dual therapy

	Onabot first	CGRP mAbs first	Full cohort
Total, *n*	171	23	194
MMDs [median (Q1–Q3)]			
Before treatment	30 (30–30)	30 (20–30)	30 (30–30)
After first therapy	19 (12–30)	15 (15–30)	15 (12–30)
After dual therapy	12 (3–20)	7 (3–28)	8 (3–22)
First-therapy reduction, days	10 (0–16)	1 (0–15)	10 (0–15)
Dual-therapy reduction, days	20 (6–26)	13 (0–18)	18 (5–26)
Improvement [median (Q1–Q3)]			
First-therapy improvement, %	33 (0–60)	7 (0–50)	33 (0–56)
Dual-therapy improvement, %	50 (0–73)	33 (0–80)	50 (0–73)
Dual-therapy total improvement, %	73 (22–87)	50 (0–87)	73 (17–87)
≥ 50% [*n* (%)]	118 (69.0)	14 (60.9)	132 (68.0)
≥ 75% [*n* (%)]	80 (46.8)	10 (43.5)	90 (46.4)

MMDs monthly migraine days, *Onabot* onabotulinumtoxinA, *CGRP mAbs* anti-calcitonin gene-related peptide monoclonal antibodies, *Onabot first* dual-therapy patients who received onabotulinumtoxinA first before adding anti-CGRP monoclonal antibodies, *Q1–Q3* quarter 1–quarter 3 (interquartile range), *CGRP mAb first* dual-therapy patients who received anti-CGRP monoclonal antibodies first before adding onabotulinumtoxinA

Table 3 Dual-therapy analysis of monthly migraine days

Statistical tests	Onabot first	CGRP mAbs first	Full cohort
Friedman ANOVA *p*-value	< 0.0001	< 0.0001	< 0.0001
MMDs [median (95% CI)]			
Baseline	30 (27.7–28.9)	30 (22.4–28.3)	30 (27.3–28.6)
First therapy	19 (17.2–19.9)	15 (14.8–22.4)	15 (17.3–19.8)
Dual therapy	12 (10.3–13.6)	7 (7.7–18.1)	8 (10.5–13.6)
Dunn's multiple comparison *p*-value MMDs			
Baseline vs. after first therapy	< 0.0001	0.122	< 0.0001
Baseline vs. after dual therapy	< 0.0001	< 0.0001	< 0.0001
After first therapy vs. after dual therapy	< 0.0001	0.008	< 0.0001
Wilcoxon matched-pairs signed rank *p*-value Reduction of MMD			
First therapy vs. dual therapy	< 0.0001	< 0.0001	< 0.0001

ANOVA analysis of variance, *CI* confidence interval, *MMDs* monthly migraine days, *Onabot* onabotulinumtoxinA, *anti-CGRP mAb* anti-calcitonin gene-related peptide monoclonal antibodies, *Onabot first* dual-therapy patients who received onabotulinumtoxinA first before adding anti-CGRP monoclonal antibodies, *CGRP mAb first* dual-therapy patients who received anti-CGRP monoclonal antibodies first before adding onabotulinumtoxinA

of the consecutive monotherapy group ($n = 229$) are summarized in Table 4. The median age for patients with consecutive monotherapy was 47 (39–57) years. Most of the patients in this group were female (88.2%). The dataset had 83.4% of patients diagnosed with migraine without aura. During their anti-CGRP mAb monotherapy, the specific mAbs used were erenumab for 63.8% of patients, galcanezumab for 19.2% of patients, and fremanezumab for 17% of patients.

3.4 Comparison of Consecutive Monotherapy and Dual Therapy

Within the consecutive monotherapy sample, onabot monotherapy decreased the MMDs from a baseline of 30 (25–30) to 15 (8–25). Anti-CGRP mAb monotherapy went from 25 (15–30) MMDs at baseline to 12 (4–25) MMDs (Table 4). A significant difference was found between the reduction of MMDs from anti-CGRP mAb monotherapy and onabot monotherapy ($p = 0.04$), dual therapy and

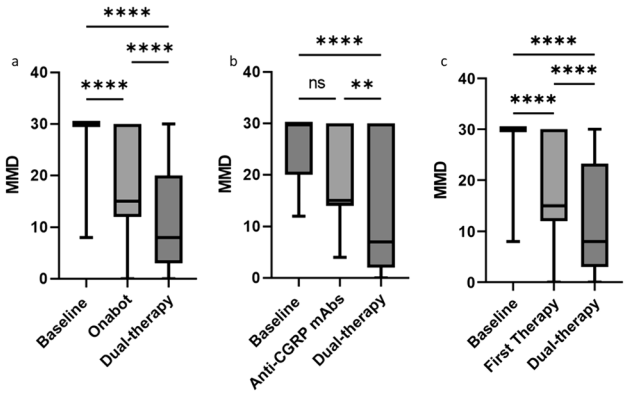

Fig. 2 Monthly migraine frequency before and after therapies. **a** Baseline MMDs, MMDs after onabot first therapy, followed by changes in MMDs after a minimum of 3 months of dual therapy. **b** Baseline MMDs, MMDs after anti-CGRP mAbs-first therapy, followed by changes in MMDs after a minimum of 3 months of dual therapy. **c** Baseline MMDs, MMDs following first therapy (with either onabot or anti-CGRP mAbs), followed by changes in MMDs after a minimum of 3 months of dual therapy. All boxplot whiskers display the minimum to maximum values. Significance shown above. **** indicates $p < 0.0001$, ** indicates $p < 0.01$, *ns* indicates non-significant or $p > 0.05$. *MMDs* monthly migraine days, *onabot* onabotulinumtoxinA, *anti-CGRP mAb* anti-calcitonin gene-related peptide monoclonal antibodies

anti-CGRP mAb monotherapy ($p < 0.0001$), and dual therapy compared with onabot monotherapy ($p < 0.0001$) (Table 5, Fig. 3). This difference was also seen when combining the two consecutive monotherapy groups and comparing with dual therapy using a Mann–Whitney test ($p < 0.0001$) (Table 5, Fig. 3b).

4 Discussion

Our results demonstrate that concurrent anti-CGRP and onabot therapy significantly reduces MMDs in chronic migraine patients treated at the Cleveland Clinic, when compared with monotherapy alone. These results were consistent when comparing the first therapy and dual therapy within a single group of patients who experienced both treatment conditions, as well as when comparing patients who received dual treatment with a separate group of patients who received consecutive monotherapy.

The prophylactic treatment of migraine has evolved dramatically with the addition of onabot in 2010, followed by the anti-CGRP mAbs beginning in 2018. Although concurrent use has been largely limited by insurance approval, there is surmounting evidence that their combined use leads to reduced headache frequency and disability. Our study is a retrospective chart review analyzing the concomitant use of onabot and anti-CGRP mAbs performed at one of the largest headache centers in the United States.

To date, the two largest real-world studies on combined use of anti-CGRP mAbs and onabot performed at private practice headache centers showed a reduction in monthly headache days (MHDs) [34, 35]. The study performed by Blumenfeld et al. (October 2018–November 2019 study timeline) demonstrated 25.7% ($n = 218$) of patients and 36.7% ($n = 180$) of patients experienced a $\geq 50\%$ reduction in MHDs after approximately 3 and 6 months of dual therapy, respectively [34]. Similarly, the retrospective chart review ($n = 148$) performed by Mechtler et al. (June 2018–March 2020 study timeline) demonstrated that 21.2% of patients had a $\geq 50\%$ reduction in MHD and 4.4% had a $\geq 75\%$ reduction in MHD after 3 months of combined treatment with anti-CGRP mAbs and onabot [35]. In our study, we found that 68.0% (132/194) of patients had a $\geq 50\%$ reduction in MMDs and 46.4% (90/194) had a $\geq 75\%$ reduction in MMDs after a minimum of 3 months of dual therapy (Table 2). These studies may demonstrate a lower benefit of combined use of anti-CGRP mAbs and onabot, as our study focused on MMDs rather than MHDs, to better target and observe the impact on migraines specifically. Additionally, these studies looked specifically at anti-CGRP mAbs being added to onabot and did not include patients with anti-CGRP mAbs adding onabot; however, we included both routes of dual therapy. A retrospective cohort study by Nandyala et al. examining combined treatment of onabot and erenumab ($n = 50$) demonstrated that combined treatment presented a significantly lower number of MMDs than onabot treatment alone (11.3 ± 9.3 vs. 14.9 ± 9.4; $p < 0.001$) as well as a significantly lower number of MHDs than onabot treatment alone (18.2 ± 10.3 vs. 20.7 ± 9.1; $p = 0.042$) [36]; however, that study only looked at 1 month of combined use.

In our study, 58.8% (114/194) of the dual-therapy patients were prescribed erenumab, 22.2% (43/194) were prescribed galcanezumab, and 19.1% (37/194) were prescribed fremanezumab. In the aforementioned studies, 77.8% (200/257) of patients were prescribed erenumab, 16.3% (42/257) were prescribed galcanezumab, and 5.8% (15/257) were prescribed fremanezumab, while in the second study, 56.7% (84/148) of patients were prescribed erenumab, 0.7% were prescribed galcanezumab (1/148), and 42.6% were prescribed fremanezumab (63/148) [34, 35]. Therefore, our study has a higher percentage of patients receiving galcanezumab and fremanezumab, which bind the CGRP ligand, whereas erenumab binds to the receptor, which may reflect differences in outcomes.

Unlike the previous studies, we compared the dual-therapy dataset with a separate consecutive monotherapy group. There was a significant difference in the MMD reductions between monotherapy of onabot, anti-CGRP mAb monotherapy, and the dual-therapy groups ($p < 0.0001$). The MMD reduction comparison of onabot monotherapy and dual therapy proved significantly different ($p < 0.0001$) and anti-CGRP mAb and dual therapy were found to be significantly different ($p < 0.0001$). Overall, dual therapy

Table 4 Characterization of consecutive monotherapy dataset and treatment outcomes

Demographic variables	Consecutive monotherapy
Total, *n*	229
Sex	
Female	202 (88.2)
Male	27 (11.8)
Age, years [median (Q1–Q3)]	47 (39–57)
Racial background	
American Indian/Alaska Native	–
Asian	1 (0.4)
Black	11 (4.8)
Multiracial/multicultural	8 (3.5)
White	205 (89.5)
Other	4 (1.7)
Migraine type	
Migraine without aura	191 (83.4)
Migraine with aura	38 (16.6)
Anti-CGRP mAbs	
Erenumab	146 (63.8)
Galcanezumab	44 (19.2)
Fremanezumab	39 (17.0)
Eptinezumab	0 (0)
MMDs [median (Q1–Q3)]	
Before onabot monotherapy	30 (25–30)
After onabot monotherapy	15 (8–25)
Reduction from onabot monotherapy	10 (1–18)
Before anti-CGRP mAb monotherapy	25 (15–30)
After anti-CGRP mAb monotherapy	12 (4–25)
Reduction from anti-CGRP mAb monotherapy	7 (0–15.5)
Improvement	
Onabot monotherapy improvement percentage [median (Q1–Q3)]	48 (3.3–66.7)
≥ 50% from onabot monotherapy	113 (49.3)
≥ 75% from onabot monotherapy	38 (16.6)
Anti-CGRP mAb monotherapy improvement percentage [median (Q1–Q3)]	35 (0–66.7)
≥ 50% anti-CGRP mAb monotherapy	104 (45.4)
≥ 75% from anti-CGRP mAb monotherapy	45 (19.7)

Data are expressed as *n* (%) unless otherwise specified

Q1–Q3 quarter 1–quarter 3 (interquartile range), *MMDs* monthly migraine days, *Onabot* onabotulinumtoxinA, *anti-CGRP mAbs* anti-calcitonin gene-related peptide monoclonal antibodies

shows improvement in MMDs compared with monotherapy of either treatment. In addition, we found a significant difference ($p = 0.04$) between anti-CGRP mAb monotherapy and onabot monotherapy, which may be because the onabot group is skewed towards people who took onabot for a longer time, which is more indicative of a strong positive response. Although, there is a larger median reduction of MMD from onabot monotherapy (10 [1–18] onabot vs. 7 [0–15.5]), we see a slightly higher percentage of anti-CGRP mAb monotherapy patients who experienced a ≥ 75% (16.6% onabot vs. 19.7% anti-CGRP mAb) improvement in MMD frequency. This may suggest that patients respond better to onabot generally, but those who benefit from anti-CGRP mAbs have larger margins of improvement.

Onabot is administered every 12 weeks according to the PREEMPT paradigm. However, a wear-off phenomenon has been demonstrated as early as week 8, prior to the next treatment session, resulting in increased moderate to severe

Table 5 Comparison of reduction in MMDs for consecutive monotherapy and dual therapy n

Statistical tests	*p*-value
Kruskal–Wallis test	<0.0001
Reduction in MMDs [median (95% CI)]	
Onabot monotherapy	10 (9.8–12.1)
Anti-CGRP mAb monotherapy	7 (7.7–10.1)
Dual therapy	18 (14.4–17.4)
Dunn's comparison	
Reduction in MMDs	
Onabot monotherapy vs. anti-CGRP mAb monotherapy	0.04
Onabot monotherapy vs. dual therapy	< 0.0001
Anti-CGRP mAb monotherapy vs. dual therapy	< 0.0001
Mann–Whitney test	
Reduction in MMDs	
Monotherapy vs. dual therapy	< 0.0001
Monotherapy [median (95% CI)]	9.5 (9.1–10.8)
Dual therapy [median (95% CI)]	18 (14.4–17.4)

CI confidence interval, *MMDs* monthly migraine days, *Onabot* onabotulinumtoxinA, *anti-CGRP mAb* anti-calcitonin gene-related peptide monoclonal antibodies

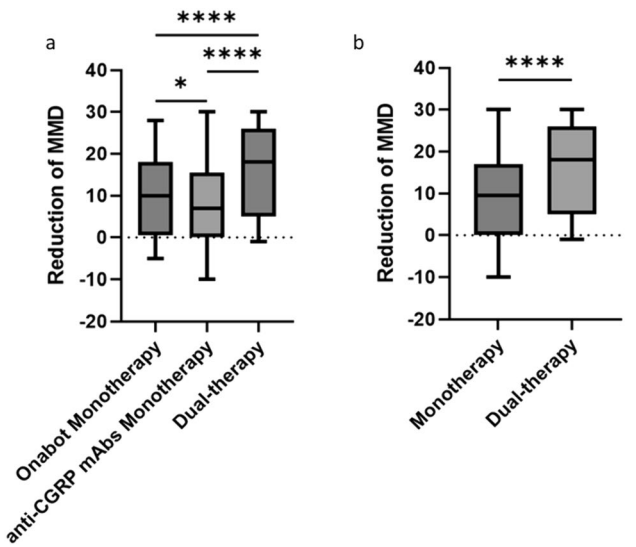

Fig. 3 Reduction of MMDs for consecutive monotherapy groups (onabot and anti-CGRP mAb monotherapy) and dual therapy. **a** The reduction of MMDs for patients treated with onabot monotherapy, anti-CGRP mAb monotherapy, and those with concurrent onabot and anti-CGRP mAb—our dual-therapy cohort. **b** Monotherapy of anti-CGRP mAb or onabot compared with dual therapy of anti-CGRP mAb and onabot. All boxplot whiskers display the minimum to maximum values. Significance shown above. **** indicates $p < 0.0001$, * indicates $p = 0.04$. *MMDs* monthly migraine days, *onabot* onabotulinumtoxinA, *anti-CGRP mAb* anti-calcitonin gene-related peptide monoclonal antibodies

migraine days, number of rescue medications used, and number of emergency room visits [37–39]. A retrospective chart review by Masters-Irailov and Robbins demonstrated wear-off in 62.9% (90/143) of patients receiving onabot for chronic migraine, most commonly 2–4 weeks prior to the next injection (43.3%) and after the very first injection (40.0%) [37]. Our study found 50.5% of patients experiencing wear-off at 2 (2–4) weeks prior to the next onabot injection. A retrospective chart review performed by Ozudogru et al. ($n = 36$) demonstrated that there is a potential benefit of anti-CGRP mAbs in delaying the wearing-off of onabot by an average of 2 weeks when used in combination, thus extending the therapeutic benefit of onabot [40].

Our study shows further evidence that concomitant use of anti-CGRP mAbs and onabot leads to improved migraine frequency. Due to the differences in administration and eptinezumab's later FDA approval date, the anti-CGRP mAb intravenous infusion was not included in our patient population. Limitations of this study include the limited follow-up period (post-prescription follow-up appointments have predetermined timelines generally); the standard follow-up for both onabot and anti-CGRP mAbs is approximately every 3 months initially. However in practice, scheduling conflicts and availability of appointments may adjust or delay the follow-ups. In the chart review, the appointment timelines were noted and confirmed to have met the inclusion criteria. Additionally, there is variation of onabot administration among providers (ranging from 155 to 200 units within the muscle groups included in the PREEMPT protocol) that can introduce some noise into the dataset. Furthermore, the nature of a real-world retrospective chart review can be inaccurate or inconsistent. A thorough manual check of each individual patients' charts was conducted to ensure the most accurate data were extracted, and the templated notes provided further consistency. The resulting datasets for the dual-therapy and consecutive monotherapy groups had no missing data. Of note, we also sought to evaluate whether sequence of therapy made a difference. Since anti-CGRP mAbs first gained FDA approval in 2018, the majority of patients were started on onabot first, and therefore the results in the anti-CGRP mAb-first group were likely limited by lack of power. Future randomized controlled trials should be considered to further assess their combined use.

5 Conclusions

Combination therapy of anti-CGRP mAbs and onabot is more efficacious than monotherapy in chronic migraine patients. Our study adds to the evidence that their combined use leads to a better reduction in migraine frequency and is the first to compare the treatment outcomes with a separate monotherapy patient population.

Declarations

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Conflict of Interest Amira Salim, Elise Hennessy, Claire Sonneborn, Olivia Hogue, Sudipa Biswas, MaryAnn Mays, Aarushi Suneja, Zubair Ahmed, and Ignacio F. Mata have no disclosures to declare relevant to this manuscript.

Ethics Approval This study was approved by the Cleveland Clinic Institutional Review Board (CC IRB), and due to the use of pre-existing data, the CC IRB waived the written informed consent.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Data Availability Due to reasons of patient data sensitivity, the data cannot be found openly available; however, the dataset will be anonymized and made available from the authors upon reasonable request from qualified investigators.

Code Availability Not applicable.

Author Contributions AS: Conceptualization, methodology, formal analysis, writing—original draft preparation, writing—review and editing, visualization. EH: Writing—original draft preparation, writing—review and editing, visualization. CS: Methodology, formal analysis, writing—review and editing. OH: Methodology, formal analysis, writing—review and editing. SBs: Writing—review and editing. MAM: Writing—review and editing, supervision. AS: Writing—review and editing. ZA: Conceptualization, writing—review and editing, supervision, funding acquisition. IFM: Writing—review and editing, supervision, project administration, funding acquisition.

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