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Predictive factors of response to anti-CGRP pathway drugs in people with multiple sclerosis

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Abstract

Background Migraine is common in people with multiple sclerosis (PwMS) and substantially contributes to disability and impaired quality of life. Although (CGRP)–targeting therapies have reshaped migraine prevention, evidence on their use in PwMS remains scarce, particularly in people receiving concomitant disease-modifying therapies (DMTs).

Methods We retrospectively collected data from 17 Italian multiple sclerosis (MS) centers on adult PwMS with comorbid migraine treated with anti-CGRP monoclonal antibodies or gepants in addition to stable DMTs. Monthly headache days (MHDs) and total number of analgesics per month were compared between treatment initiation and last follow-up. MS activity was assessed through clinical relapses, Expanded Disability Status Scale (EDSS), and MRI findings. A $\geq 50\%$ reduction in MHDs defined treatment response. Multivariate regression models were used to explore predictors of response to anti-CGRP therapies.

Results Fifty-four patients were included (46 women; mean age 42.3 years; 85% relapsing MS). Baseline MHDs averaged 19.87 ± 6.97 and declined to 11.40 ± 9.35 at follow-up ($p < 0.001$), with a parallel decrease in analgesic use ($p < 0.001$). Responder rate at the last follow-up was 53.7%. MS disease activity remained stable, with no significant changes in relapse rate, EDSS score, or MRI activity. Higher baseline headache burden was associated with greater reduction in MHDs ($\beta = +0.685$, $p < 0.001$), whereas longer MS duration predicted poorer response (OR 1.43, 95%CI 1.06–1.92, $p = 0.016$). Mild adverse events occurred in four patients (7%), without treatment discontinuation.

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Conclusion Anti-CGRP pathway therapies provided meaningful migraine improvement in PwMS while maintaining MS stability. MS disease duration and baseline headache frequency may influence therapeutic response to anti-CGRP drugs in PwMS.

Clinical trial number Not applicable

Keywords Migraine, Multiple sclerosis, CGRP, Disease-modifying therapies

Introduction

Migraine has been increasingly recognised as one of the most disabling neurological disorders, with a prevalence of approximately 15% in the general population. This condition is typically characterized by recurrent attacks of moderate to severe pain, frequently associated with photophobia, phonophobia, nausea, and vomiting [1, 2]. In people with multiple sclerosis (PwMS), this prevalence appears to be substantially higher, approaching approximately 30%, with headache onset often preceding the clinical diagnosis of MS, suggesting it may represent an early accompanying feature [3, 4]. This may be due to dysregulation of inflammatory cytokines and disrupted connectivity between brain regions involved in pain modulation, or to lesions affecting structures implicated in pain transmission and modulation, including the periaqueductal gray (PAG) and related nociceptive pathways [5, 6].

In recent years, innovative pharmacological treatments, such as calcitonin gene-related peptide (CGRP)-targeted therapies, have significantly improved the quality of life of patients with migraine [7, 8]. This class of drugs targets the CGRP pathway, a key vasodilatory neuropeptide system involved in migraine pathophysiology, and comprises both monoclonal antibodies directed against CGRP or its receptor (anti-CGRP mAbs) and small-molecule CGRP receptor antagonists (gepants) [9–11]. Anti-CGRP (mAbs) are used for preventive therapy and may be administered either subcutaneously (erenumab, galcanezumab, fremanezumab) [12, 13] or intravenously (eptinezumab), the latter offering a more rapid onset of action owing to its pharmacokinetic profile [14–16]. In parallel, gepants are a newer class of CGRP-targeting drugs that can be used for both acute (rimegepant, ubrogepant and zavegepant) and preventive (atogepant and rimegepant) migraine treatment [17].

Given their established efficacy and favourable safety profile, these agents have been largely prescribed to PwMS and migraine, with emerging evidence suggesting acceptable safety and effectiveness even in patients receiving disease-modifying therapies (DMTs), often mAbs themselves, thereby raising the issue of dual mAb therapy. Indeed, combining anti-CGRP agents with DMTs raises relevant theoretical and practical concerns. First, CGRP itself possesses potent immunomodulatory properties, including the regulation of cytokine

production and the modulation of T-cell differentiation (e.g., Th1 and Th17 pathways), and has been shown to exert anti-inflammatory and neuroprotective effects in neuroinflammatory models such as experimental autoimmune encephalomyelitis (EAE) [18]. Consequently, there is a theoretical risk that blocking the CGRP pathway could alter, directly or indirectly, the immune balance in the central nervous system, potentially antagonizing the therapeutic goals of DMTs or worsening MS disease activity. Second, the concurrent administration of two mAbs raises questions regarding cumulative immunogenicity, such as an increased risk of developing anti-drug antibodies, and the potential for overlapping systemic side effects or altered clearance mechanisms [19]. Finally, the use of oral gepants introduces potential risks of pharmacokinetic drug-to-drug interactions with oral DMTs; for instance, atogepant is primarily metabolized by the hepatic cytochrome P450 enzyme CYP3A4, requiring caution when co-administered with other substrates or inhibitors of this pathway [20]. However, to date, the available evidence remains limited and is primarily based on small-sample studies, without inclusion of patients treated with more recently approved anti-CGRP mAbs (i.e., eptinezumab) and gepants [21, 22]. Furthermore, efforts are needed to identify which patients are more likely to benefit from these novel treatments [23].

The primary aim of this study is to identify clinical or treatment-related factors that may predict the therapeutic response to anti-CGRP pathway drugs in PwMS. The secondary objective is to evaluate the safety and effectiveness of anti-CGRP drugs in PwMS and the effect of the concurrent administration of anti-CGRP drugs and DMTs in this population.

Methods

Study design

In this retrospective study, we included patients from seventeen Italian MS centres, with a concomitant diagnosis of migraine and MS, stably treated with a DMT combined with an anti-CGRP drug.

Inclusion criteria for the study were: age ≥ 18 years; diagnosis of MS according to 2017 revisions of the McDonald criteria [24]; concomitant diagnosis of migraine according to the International Classification of Headache Disorders (ICHD-3) [25], in treatment with anti-CGRP drugs for at least three months (or less in

case of discontinuation for any reason - atogepant was the only gepant available in Italy for preventive treatment during the study period); in stable treatment with DMT for MS (mAb or small molecule) for at least three months before initiation with any anti-CGRP drugs.

Episodic migraine (EM) was defined as migraine occurring on fewer than 15 days per month. Chronic migraine (CM) and medication-overuse headache (MOH) were diagnosed according to ICHD-3 criteria [25].

Exclusion criteria included incomplete or unavailable brain and/or spinal MRI (see below), insufficient clinical data, any change or poor adherence to the DMT in the three months preceding the introduction of anti-CGRP therapy, as well as modifications to concurrent migraine preventive treatments during the anti-CGRP therapy.

The observation window for each patient spanned from one year prior to the start of the anti-CGRP agent, through the baseline visit (initiation of anti-CGRP therapy), and up to the most recent follow-up during combined treatment. All adverse events (AEs) occurring during this period were documented, along with reasons for stopping either the anti-CGRP drug or the DMT. The headache and MS specialists jointly evaluated whether any AE was linked to the discontinuation of either therapy.

The study conforms to the ethical guidelines of the Declaration of Helsinki (1975). The study received approval from the Ethical Committee of Università Cattolica del Sacro Cuore in Rome (ID 4390) and was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [26].

Variables collected

Demographic and clinical information were collected for all patients.

Regarding MS, the dataset included: age at disease onset, MS phenotype (relapsing or progressive MS), prior DMT exposure, the specific DMT used alongside the anti-CGRP drug, duration of the ongoing DMT, Expanded Disability Status Scale (EDSS) score, MRI activity (defined as new T2-weighted or Gd-enhancing lesions (Gd+)), and clinical relapses (episodes of neurological symptoms lasting at least 24 h, occurring ≥ 30 days after a previous event, and not associated with fever or infection).

Brain MRI was performed at all participating centers at a minimum field strength of 1.5 Tesla, with acquisitions including at minimum T2-weighted, fluid-attenuated inversion recovery (FLAIR), and pre- and post-gadolinium T1-weighted sequences. For the purposes of this retrospective study, only MRI examinations meeting these minimum technical requirements were considered eligible for radiological assessment.

Migraine-related variables were also documented, including: migraine diagnosis (EM, CM, MOH), disease duration and age at onset, presence of aura, the anti-CGRP pathway drug prescribed (fremanezumab, erenumab, galcanezumab, eptinezumab, or atogepant) and its treatment duration, any additional migraine preventive therapies, types of acute medications used, monthly headache days (MHDs), and absolute monthly number of analgesics (AMNs). MHDs and AMNs were assessed at two time points: baseline (start of anti-CGRP therapy) (T0) and at the latest available follow-up (T1).

Outcome measures

Regarding MS, outcome measures included the EDSS score, MRI activity (new T2-weighted lesions and/or new T1-weighted Gd+ lesions), and clinical relapses. The first two were collected at three time points: 12 months before starting anti-CGRP drug (T -1), at baseline (T0), and the last follow-up of concomitant treatment (T1). Two time points were considered for clinical relapses: during 12 months before the initiation of anti-CGRP drug and during the period of concomitant therapy with anti-CGRP drugs and DMT. For migraine outcomes, a comparison of MHDs and AMNs from the baseline to the last follow-up was made. Based on the reduction in MHDs from baseline to last follow-up, we evaluated the response rate by categorizing patients as follows: non-responders ($< 30\%$ reduction), low responders ($\geq 30\%$), responders ($\geq 50\%$), super-responders ($\geq 75\%$), and migraine freedom (100% reduction). Finally, for both diseases, a combined outcome included the percentage of patients who discontinued the DMT or anti-CGRP drug for any reason.

Statistical analysis

The sample size was not defined a priori through statistical power calculations; instead, all consecutive patients meeting the inclusion criteria were enrolled. To complement the retrospective design and the absence of an a priori sample size calculation, a posteriori analysis calculating the unadjusted Number Needed to Treat (NNT) for the primary response outcome ($\geq 50\%$ reduction in MHDs) was performed. NNT was calculated as the inverse of the response rate. Continuous variables were summarized using mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), while categorical variables were presented as counts and percentages. Normality was assessed with the Shapiro–Wilk test. Subsequently, based on data distribution, comparisons between groups were performed using independent sample *t* tests for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. A multivariate binomial logistic regression model was applied to assess the association between the predictors and treatment response ($\geq 50\%$ reduction). Results of the

logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals. In addition, a multivariate linear regression model was performed to assess the association between clinical and demographic variables and the change in monthly migraine days (delta from T0 to T1), treated as a continuous dependent variable. Regression coefficients (β) with corresponding 95% confidence intervals were reported. Statistical significance was set at two-tailed $p < 0.05$. Given the retrospective design, missing data were handled using a complete-case analysis approach. Consequently, patients with missing or incomplete headache diaries at the follow-up evaluation were excluded from the effectiveness analysis, without applying data imputation techniques. Jamovi software version 2.6 was used for data analyses and for figures [27].

Results

Baseline characteristics

A cohort of 54 patients diagnosed with both MS and migraine was included from 17 different MS clinics. All patients received concurrent treatment with an anti-CGRP drug and a DMT for MS. Among these patients, 46 (85.0%) were identified with relapsing MS (RMS), while 8

(14.0 %) had progressive MS (PMS). The mean age of the cohort was 42.33 ± 9.46 years, comprising 46 females and 8 males. The average age at MS onset was 28.80 ± 10.08 years, whereas the mean age at migraine onset was 18.68 ± 7.95 years. Twenty-four patients (44.0%) at baseline had a diagnosis of CM, while sixteen patients (30%) experienced EM and fourteen patients (26.0%) had a diagnosis of MOH. Additionally, five patients (9.0%) had a diagnosis of migraine with aura. At baseline, the MHDs were 19.87 ± 6.97 . Demographics and clinical features at baseline are summarized in Table 1.

Regarding DMTs, $n = 13$ (24.0%) received ocrelizumab, $n = 11$ patients (20.0%) were administered natalizumab, $n = 9$ (17.0%) dimethyl fumarate, $n = 4$ (7.0%) ofatumumab, $n = 3$ (6.0%) were treated with teriflunomide, $n = 3$ (6.0%) fingolimod, $n = 3$ (6.0%) cladribine, $n = 2$ (3.0%) were treated with ponesimod, $n = 2$ (3.0%) glatiramer, $n = 1$ (2.0%) interferon, $n = 1$ (2.0%) siponimod, $n = 1$ (2.0%) ozanimod, and $n = 1$ (2.0%) with peginterferon beta-1a. The anti-CGRP drug prescribed included erenumab ($n = 19$, 35.0%), galcanezumab ($n = 17$, 31.0%), fremanezumab ($n = 12$, 22.0%), atogepant ($n = 3$, 6.0%), and eptinezumab ($n = 3$, 6.0%). The mean duration from DMT initiation to the addition of anti-CGRP drug as an adjunctive therapy was 52.43 ± 41.74 months.

Table 1 Demographics and clinical features at baseline

Demographics and clinical features	
Age (years), mean $\pm$ SD	42.33 $\pm$ 9.46
Sex, n (%)	46 F (85%)
Psychiatric comorbidities, n (%)	9 (16%)
Other comorbidities, n (%)	16 (29%)
Migraine features	
Age at onset, mean $\pm$ SD	18.68 $\pm$ 7.95
Aura, n (%)	5 (9%)
Chronic migraine, n (%)	24 (44%)
Medication overuse headache (MOH), n (%)	14 (25%)
Monthly headache days (MHDs), mean $\pm$ SD	19.87 $\pm$ 6.97
Number of analgesics (AMNs), mean $\pm$ SD	23.33 $\pm$ 15.12
Multiple Sclerosis features	
Age at onset, mean $\pm$ SD	28.80 $\pm$ 10.08
Months since the start of the current DMT, mean $\pm$ SD	65.17 $\pm$ 44.05
Number of relapses one year prior anti-CGRP mAbs, mean $\pm$ SD	0.16 $\pm$ 0.47
EDSS score one year prior anti-CGRP mAbs, mean $\pm$ SD	2.32 $\pm$ 1.63
Number of new T2 and/or T1-weighted Gd+ MRI lesions in the year prior anti-CGRP mAbs, mean $\pm$ SD	0.06 $\pm$ 0.24

Abbreviations: anti-CGRP mAbs = anti-calcitonin gene-related peptide monoclonal antibodies; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; F = female; Gd+ = gadolinium-enhancing; MRI = magnetic resonance imaging; SD = standard deviation; T1 = T1-weighted magnetic resonance imaging sequence; T2 = T2-weighted magnetic resonance imaging sequence

Effectiveness of anti-CGRP drugs and clinical predictors of response

The effectiveness analysis was performed in 52 patients with available headache diary data. At the observation time point (T1), the MHDs were significantly reduced from 19.87 ± 6.97 to 11.40 ± 9.35 ($p < 0.001$) as well as AMNs (23.33 ± 15.12 vs. 8.72 ± 13.58 , $p < 0.001$) (Fig. 1). Eighteen patients (35.0%) were categorized as non-responders ($< 30\%$ reduction), five (9.5%) as low responders ($\geq 30\%$ reduction), nineteen (36.5%) as responders ($\geq 50\%$ reduction), eight (15.0%) as super responders ($\geq 75\%$ reduction) and two (4.0%) as complete responders (100% reduction) (Fig. 2). Regarding the specific use of gepants, three patients received atogepant for preventive purposes. Among them, one patient achieved a robust therapeutic response with an 83.3% reduction in MHDs (super-responder) while undergoing concurrent treatment with the DMT ofatumumab. The remaining two patients, both treated with stable dimethyl fumarate, exhibited lower reduction rates in MHDs (16.67% and 22.22%, respectively), failing to meet the primary response threshold. Atogepant was well tolerated by all three participants, with no AEs reported. The overall responder rate was 53.7%. Based on this response rate, the NNT to achieve a $\geq 50\%$ reduction in MHDs in one patient was 1.86 (rounded to 2.0).

During the follow-up period (mean 12.51 ± 9.63 months), no significant difference was observed in the

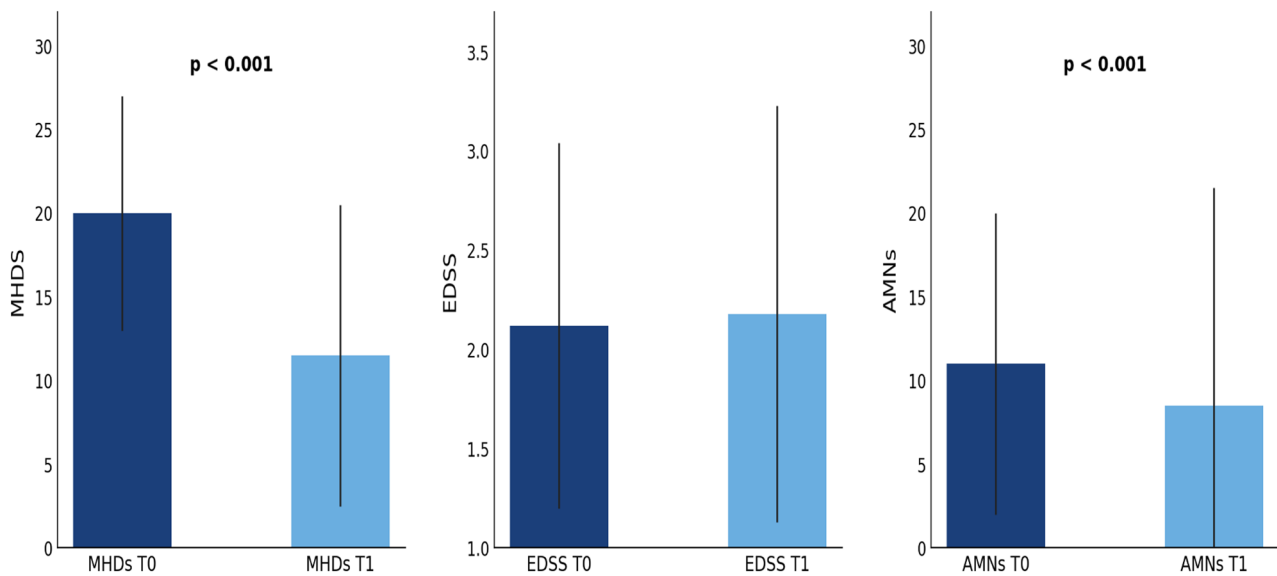


Fig. 1 Monthly headache days (MHDs), Expanded Disability Status Scale (EDSS), and number of analgesics per month (AMNs) at baseline (T0) and last follow-up (T1)

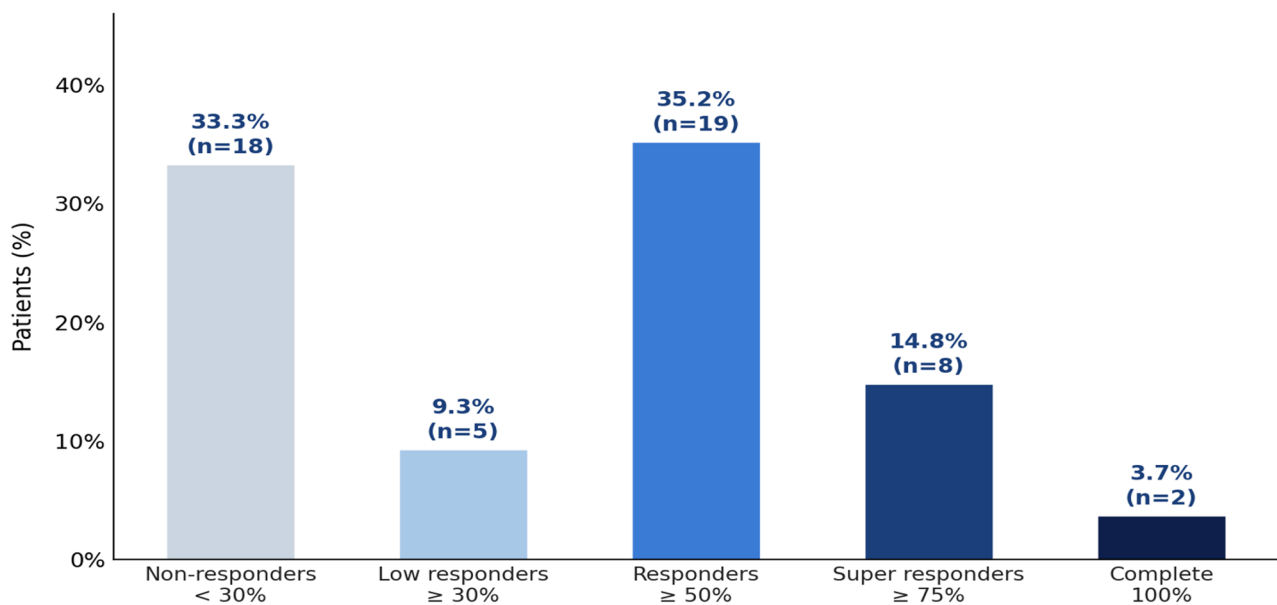


Fig. 2 Response rate to anti-CGRP therapies in patients receiving concomitant anti-CGRP therapies and disease-modifying therapies (DMTs)

proportion of patients experiencing at least one relapse (McNemar test, $p=1.0$) or in the number of relapses (Wilcoxon signed-rank test, $p=1.0$) between the year before treatment and the treatment period. The EDSS scores also remained stable throughout follow-up (2.32 ± 1.63 vs. 2.38 ± 1.67 , $p=0.42$), indicating no progression of disability. MRI activity was stable as well: no significant differences were observed in the proportion of patients with new T2 and/or T1-weighted gadolinium-enhancing lesions across the evaluated time points (McNemar test, $p=1$). Comparing responders ($\geq 50\%$ reduction in MHD) with non-responders, responders had

a significantly different MS disease duration ($p < 0.001$) and age ($p=0.006$), whereas no significant differences were observed for the other demographic and clinical variables (Table 2).

A multivariate linear regression model was then applied ($R^2=0.491$, $p=0.002$) to assess the association between clinical variables (baseline MHDs, MS duration, migraine duration, EDSS, age, MS subtype (PMS vs. RMS), and sex) and treatment response (delta of MHDs from T0 to T1). Only baseline MHDs positively predicted treatment response ($\beta = +0.685$, $p < 0.001$), indicating that patients with a higher initial headache burden achieved

Table 2 Demographics and clinical features. responders vs. non-responders

	Responders (> 50% reduction MHDs)	Non-responders (< 50% reduction MHDs)	p-value
Demographics			
Age (years), mean $\pm$ SD	38.79 $\pm$ 9.48	46.0 $\pm$ 7.86	0.006
Sex, n (%)	19 F (36%)	25 F (48%)	0.771
Psychiatric comorbidities, n (%)	5 (9.5%)	3 (6%)	0.288
Other comorbidities, n (%)	7 (12%)	9 (16%)	0.883
Migraine features			
Age at onset, mean $\pm$ SD ^a	15.28 $\pm$ 6.43	21.42 $\pm$ 8.16	0.003
Disease duration (years), mean $\pm$ SD ^a	22.90 $\pm$ 10.97	24.88 $\pm$ 9.28	0.284
Aura, n (%) ^b	2 (4%)	3 (6%)	0.858
Episodic migraine, n (%) ^c	4 (8%)	11 (21%)	0.087
Chronic migraine, n (%) ^c	10 (19%)	13 (25.0%)	0.817
Medication overuse headache, n (%) ^c	10 (19%)	4 (8%)	0.022
Monthly headache days, mean $\pm$ SD ^d	21.04 $\pm$ 7.49	19.46 $\pm$ 6.19	0.422
Absolute number of analgesics, mean $\pm$ SD ^e	25.27 $\pm$ 15.89	18.75 $\pm$ 13.95	0.224
Multiple Sclerosis features			
Age at onset, mean $\pm$ SD ^f	28.12 $\pm$ 11.02	28.5 $\pm$ 9.69	0.595
Disease duration (years), mean $\pm$ SD ^f	8.0 $\pm$ 4.99	17.84 $\pm$ 10.03	<0.001
Months since the start of the current DMT, mean $\pm$ SD ^g	62.22 $\pm$ 46.94	72.20 $\pm$ 42.09	0.547
Prior preventive DMTs, mean $\pm$ SD ^h	2.37 $\pm$ 6.37	1.10 $\pm$ 1.16	0.674
Number of relapses one year prior anti-CGRP mAbs, mean $\pm$ SD ⁱ	0.16 $\pm$ 0.48	0.16 $\pm$ 0.48	1.00
EDSS one year prior anti-CGRP mAbs, mean $\pm$ SD ^j	2.26 $\pm$ 1.63	2.42 $\pm$ 1.62	0.794
New T2/Gd + MRI lesions one year prior anti-CGRP mAbs, n (%) ^a	2 (4%)	1 (2%)	0.525

Abbreviations: anti-CGRP mAbs=anti-calcitonin gene-related peptide monoclonal antibodies; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; F=female; Gd+=gadolinium-enhancing; MHDs=monthly headache days; MRI=magnetic resonance imaging; SD=standard deviation; T2=T2-weighted magnetic resonance imaging sequence

greater reductions in MHDs (Fig. 2). MS disease duration, EDSS, age, MS subtype, and sex did not significantly predict improvement.

Furthermore, a multivariate binomial logistic regression model was applied to identify predictors of treatment response (responder vs. non-responder). In this model, longer MS disease duration was significantly

associated with a higher likelihood of non-response to treatment (OR 1.43, 95% CI 1.06–1.92, $p=0.016$), whereas age, EDSS, MS subtype, sex, and baseline MHDs were not significantly associated with the outcome (Supplementary material).

Discontinuation rate

During the concomitant treatment period, ten patients (18.0%) discontinued anti-CGRP drugs after an average of 10.44 ± 9.53 months. Of these, four patients discontinued treatment due to migraine stable improvement, two due to poor effectiveness, one due to the onset of trigeminal neuralgia (subsequently investigated with an MRI that revealed a new active MS lesion, suggesting an MS-related event rather than a drug AEs), one due to injection site reaction, and two due to a worsening of the headache condition. Additionally, four patients discontinued DMT after an average of 38.75 ± 19.87 months: one patient due to an increased risk for developing progressive multifocal leukoencephalopathy (PML), one due to an increased infectious risk, another due to the appearance of a new asymptomatic T2-weighted brain lesion at MRI, and one patient due to the beneficial effects.

Safety and tolerability

In the overall study population of 54 patients, AEs were uncommon; only four participants (7.0%) reported mild AEs, no severe or serious AEs were observed, and none led to discontinuation. Two of them reported constipation, one nausea, and one presented irritation at the site of injection.

Discussion

In this multicenter retrospective cohort, we investigated the clinical effectiveness, tolerability, and potential predictors of response to anti-CGRP drugs in PwMS and comorbid migraine undergoing stable DMTs for MS. Our findings indicate that the concomitant use of anti-CGRP drugs and DMTs is both effective and safe, supporting the growing evidence that these two therapeutic strategies can be integrated without affecting MS disease course and stability.

The response rate to anti-CGRP drugs in our cohort of PwMS was comparable to the response rates reported in the general migraine population treated with anti-CGRP drugs, suggesting that the presence of MS does not hinder the therapeutic effect of CGRP blockade. Importantly, no clinical and/or neuroradiological MS activity was observed during our study, indicating that anti-CGRP treatment does not exacerbate MS disease activity in the medium term (mean follow-up ~ 10 months for anti-CGRP therapy), confirming data that were already emerging in smaller cohorts.

In a retrospective case series, the concurrent use of anti-CGRP mAbs and DMTs (including the combination of two mAbs) was not associated with the worsening of MS symptoms in 22 patients; only 11% of patients reported mild adverse events, and no patient reported the worsening of MS symptoms [28]. Similarly, another observational study involving 25 PwMS treated with anti-CGRP mAbs confirmed their effectiveness and good tolerability, showed no significant impact on MS disease course [21]. To date, however, data on gepants remain scarce, with only a single patient reported in a small case series of nine individuals [22]. In our cohort, three patients were treated with atogepant. Although the sample size is limited, the inclusion of gepants in this population is of clinical interest. Their oral administration and shorter half-life compared with mAbs provide a manageable pharmacokinetic profile that may minimize the risk of long-lasting interactions with concurrently administered DMTs and allow rapid treatment suspension if safety concerns or MS exacerbations arise. Clinically, the heterogeneous outcomes observed, ranging from insufficient improvement in patients on dimethyl fumarate to a substantial super-response in the patient receiving ofatumumab, highlight the necessity for broader prospective investigations to clarify whether specific combinations of small-molecule CGRP antagonists and distinct DMT classes influence therapeutic efficacy. No data are present in the literature on the use of eptinezumab in this population.

Our analysis also explored potential predictors of treatment response. Current literature on predictors of response to anti-CGRP therapies is heterogeneous and conflicting. Variability in patient populations, comorbidities, migraine characteristics, and study design likely contributes to these inconsistencies [29–31]. In our cohort, baseline migraine frequency was a significant predictor of response, indicating that patients with a higher initial migraine burden achieved greater reduction in migraine days. A longer MS disease duration was associated with reduced benefit, potentially reflecting cumulative neurological impairment or long-standing alterations in pain processing pathways [32].

A deeper analysis of the baseline characteristics further supports this hypothesis. In our cohort, responders were significantly younger and had a shorter MS disease duration compared to non-responders. This suggests that earlier intervention with anti-CGRP therapies might yield better clinical outcomes, possibly because younger patients with a more recent MS onset possess more intact central descending pain modulation networks and have accumulated less neurodegeneration. This aligns with our regression model, demonstrating that a higher initial headache burden strongly predicts a greater absolute reduction in migraine days, suggesting that patients

with more severe, chronicized forms of migraine have the widest margin for clinical improvement when treated with anti-CGRP agents.

From a safety perspective, the combination of anti-CGRP drugs in PwMS and DMTs was well tolerated. Only 7% of patients reported mild adverse events, none of which required treatment discontinuation. This is in line with previous case series suggesting that CGRP-targeting therapies have a favourable safety profile in people with MS, with low rates of AEs and no significant interactions with DMTs [21, 33, 34]. Importantly, the frequency of discontinuations due to MS-related concerns was minimal, and most discontinuations of therapy were either unrelated to safety concerns or due to favourable clinical outcomes such as migraine improvement.

These findings have several clinical implications. First, they support the safe integration of anti-CGRP therapies into the therapeutic management of PwMS who suffer from migraine, with the potential to further improve patients' quality of life. This is particularly relevant considering that commonly used traditional oral preventive treatments, such as amitriptyline, valproic acid, topiramate, and calcium channel blockers, may induce somnolence or worsen fatigue and may exacerbate cognitive or psychiatric adverse effects in a population already burdened by these symptoms or at increased risk of developing them.

Second, they highlight the importance of a detailed profiling of migraine/headache frequency and severity, yet in the MS clinics, including baseline migraine burden and disease duration, to identify patients who are more likely to benefit from treatment.

Third, the absence of negative interactions with DMTs is particularly reassuring for clinicians who manage complex cases requiring simultaneous treatment of both neurological conditions.

Altogether, these findings may support an early use of anti-CGRP therapies in this population, given their efficacy and the potential impact of longer disease duration on treatment response. Indeed, migraine and headache appear to be more prevalent in the early phases of MS and are more frequently associated with relapsing forms of the disease, which are characterized by higher inflammatory activity. This observation also could open a very preliminary discussion on the role of CGRP modulation in MS, as preclinical studies have suggested a neuroprotective role of CGRP in experimental autoimmune encephalomyelitis (EAE) [35].

Importantly, an early use of anti-CGRP therapies is already supported by American guidelines, which recommend anti-CGRP agents as first-line preventive treatments for migraine [36].

It is also worth noting that the age of migraine onset in our patients precedes the age of MS onset by about 10

years. Although the present study does not allow us to establish a causal or specifically prodromal relationship, this temporal pattern is consistent with, and may lend further support to, the growing body of evidence characterizing the MS prodromal phase, in which headache and other neurological symptoms have been reported to precede MS diagnosis by several years [37].

This study represents the largest multicenter evaluation to date with a medium- to long-term follow-up of concomitant anti-CGRP and DMT use in PwMS, including both mAbs (subcutaneous and intravenous) and gepants.

This study also has some limitations that should be acknowledged. Its retrospective design inherently limits its causal inference and makes the study susceptible to typical observational biases, including selection bias and recall bias, the latter particularly concerning the retrospective collection of baseline headache frequencies and analgesic use. Furthermore, missing data represent a common challenge in retrospective cohorts. We addressed this by performing a complete-case analysis for the primary effectiveness outcomes. While this approach avoids the assumptions required for data imputation, it may introduce a degree of attrition bias, although the impact was likely minimal given the very low number of missing diaries in our cohort ($n = 2$). The heterogeneity in both DMTs and anti-CGRP treatments may represent a limitation; nevertheless, it mirrors real-world prescribing patterns and precluded adequately powered sub-analyses by individual anti-CGRP agents (e.g., gepants or eptinezumab).

Conclusion

This study offers real-world insights suggesting that anti-CGRP therapy administered alongside DMTs in people with MS may be both effective and well-tolerated over the observed follow-up period, with clinical benefit influenced by baseline migraine frequency and MS disease duration. However, given the relatively short follow-up duration, definitive conclusions regarding long-term safety and, in particular, the absence of an effect on MS disease course, prospective studies with longer follow-up are needed to confirm these preliminary findings.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s10194-026-02435-7>.

Supplementary Material 1

Author contributions

V.N., S.C., M.R. and F.P. wrote the main manuscript text and S.C. and M.R. prepared the figures. All authors reviewed the manuscript.

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Data availability

All data supporting the results of this study are included within the article and its supplementary material. Additional datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki (1975). Ethical approval was obtained from the Ethics Committee of Università Cattolica del Sacro Cuore. All participants provided written informed consent authorizing the use of their clinical and radiological data for research purposes.

Competing interests

CV has received research support and personal fees from Angelini Pharma, Lundbeck, Jazz Pharmaceuticals, Eisai, and UCB; no other conflicts of interest related to this work are present. GAM is an Advisory Board member of Sanofi-Genzyme, Merck-Serono, Novartis, Roche, Alexion, Amgen and received honoraria for speaking or consultation fees from Almirall, Amgen, Alexion, Merck Serono, Neuraxpharm, Novartis, Sanofi-Genzyme, Roche, and BMS. She is the principal investigator in clinical trials for Merck Serono, Novartis, Roche, Sanofi-Genzyme, and BMS. LFI received financial support, consulting fees for the participation in advisory boards and support for attending meetings from: Teva, Eli Lilly, Lundbeck, Pfizer and AbbVie; he is Associate Editor for Frontiers in Neurology and junior editor of Cephalalgia and Cephalalgia report. MR has received research support and personal fees from Angelini Pharma, Lundbeck, Jazz Pharmaceuticals, Eisai, and UCB; no other conflicts of interest related to this work are present. FP received consulting fees for the participation in advisory boards from Organon, Pfizer and Lundbeck and support for attending meetings from Abbvie, Pfizer, Lundbeck, Teva, Storz. No conflicts of interest relevant to this work are reported. VT has received honoraria, travel grant, research support from Almirall, Viatrix, Novartis, Roche, Biogen, Janssen, Juvisé, Merck, Alexion, Horizon, Amgen, Bristol Myers Squibb, Lundbeck, Sanofi.

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