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Effectiveness and tolerability of rimegepant in the acute treatment of migraine: a real-world, prospective, multicentric study (GAINER study)

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Abstract

Background Rimegepant, a novel oral calcitonin gene-related peptide receptor antagonist, has been recently approved for the acute migraine treatment. While its efficacy was confirmed in randomized clinical trials, no data is available regarding real-life effectiveness and tolerability. GAINER, a prospective, multicentric study, aimed to evaluate rimegepant effectiveness and tolerability in the real-world setting.

Methods Our study involved 16 headache centers across Italy. The main outcomes were: i) 2 h pain freedom, and ii) occurrence of treatment-emergent adverse events after administration. Participants were instructed to treat one migraine attack with rimegepant 75 mg orally disintegrating tablet. Using an ad hoc diary, participants prospectively collected migraine attack features at baseline and every 30 min after rimegepant administration, up to 2 h post dose. A 24 h follow up was also collected.

Results We enrolled 103 participants with migraine (74.8% female, mean age 44.4 [42.0 – 46.7] years, 24.3% with chronic migraine of whom 44.0% presented a concomitant diagnosis of medication overuse headache). The number of previously failed preventive classes was 2.7 [2.3 – 3.2]. Participants presented a mean of 9.6 [8.2 – 10.9] monthly migraine days at baseline. At rimegepant intake, 40.8% of patients rated migraine intensity as severe. Pain freedom 2 h post dose was reported in 44.7% (46/103) of individuals. Pain freedom 2 h post dose was not influenced by baseline pain severity ($p=0.316$), but it was associated with timing of intake ($p=0.032$) with a higher rate of 2 h pain freedom when rimegepant was taken within 1 h from pain onset. Mild adverse events were reported in 15.5% total attacks (16/103), predominantly fatigue ($n=6$), gastrointestinal symptoms ($n=6$), somnolence ($n=4$), and transient cognitive difficulties ($n=3$). Tolerability was rated as good-to-excellent in 85.4% cases (88/103).

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Conclusions Our data confirms rimegepant effectiveness and safety in the acute migraine treatment in a real-world setting in a cohort of participants that includes subjects with episodic or chronic migraine, medication overuse and a high number of prior preventive treatment failures.

Trial registration The study was preregistered on clinicaltrial.gov, NCT05903027.

Keywords Acute treatments, Gepants, Triptans, CGRP

Introduction

Migraine is a common and disabling neurologic disease that affects nearly 1 billion people worldwide [1]. For decades, the acute treatment of migraine was based on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and triptans (migraine-specific 5-$HT_{1B/1D}$ receptor agonists) [2]. NSAIDs still represent the most used class, ranging between 46 and 80%, partially due to access-to-care issues [2–4]. Triptans prescription may be limited by the risk of development of medication overuse headache, adverse events, or contraindications (such as cardiovascular diseases or uncontrolled hypertension), and up to 30% of migraine individuals do not have a complete clinical response [5–7]. A recent study provided an estimate of people with migraine who might benefit from alternatives to triptans by means of general practitioners' data [8]. According to this analysis, around 30% of people with migraine had never been prescribed a triptan, and at least 11% of those seeking care in the primary setting would benefit from effective alternatives [8]. A significant proportion of subjects are dissatisfied with their acute medications, mainly due to slow onset of action, partial effectiveness, headache relapse, or side effects [9]. Furthermore, suboptimal acute management is associated with higher migraine-related disability, poor quality of life, and increased risk of evolution toward a chronic pattern and medication overuse headache [10].

Then, several unmet needs for the acute migraine management still exist, and closing this gap will represent an important step forward in improving the migraine care.

Recently, rimegepant (a small-molecule CGRP receptor antagonist) and lasmiditan (a 5-HT_{1F} receptor agonist) proved effective against placebo as acute migraine treatments in randomized clinical trials (RCTs) [11–16].

The International Headache Society practice recommendations support the use of gepants in migraine individuals without optimal response to triptans or combination therapy, or in subjects with contraindications to triptans [17]. Indeed, gepants may be effective in patients not responding to triptans owing to their different mechanism of action. In addition, although the effects related to long-term CGRP antagonism are yet to be elucidated, labels for gepants do not report specific contraindication in patients with cardiovascular diseases [18].

Rimegepant is the only molecule approved for both acute and preventive migraine treatment [11]. In the acute treatment it is administered as a 75 mg dose no more than once a day and it proved superior to placebo for different outcomes (*e.g.,* freedom from pain and associated symptoms at 2 h follow-up), with a good safety and tolerability profile [19–21]. However, it is important to note that all the RCTs on rimegepant as acute migraine treatment only included individuals with episodic migraine, while no data exists on subjects with chronic migraine [22]. To date, no observational, real-world studies have been conducted to assess the effectiveness of rimegepant in the acute treatment of migraine. Real world studies are useful because they provide information on populations that may not have been included in RCTs and to provide evidence in a context similar to daily clinical practice.

The primary objective of the multicentric GAINER study is to assess the effectiveness and tolerability of rimegepant 75 mg orally disintegrating formulation in the acute treatment of migraine in the real-world setting.

Methods

Study design, patient features and variables collected

GAINER is a real-world, prospective, multicentric study, including all consecutive out-patients that treated at least one migraine attack with rimegepant 75 mg orally disintegrating tablet (ODT).

In the GAINER study, participants were instructed to treat up to 4 migraine attacks. In this paper we report the effects of rimegepant on the first-treated migraine attack. The study was pre-registered on clinicaltrial.gov (NCT05903027) and the Italian centers involved are reported in Supplementary Table 1.

The study was approved as part of the *Registro Italiano Cefalee (RICe)* study by the local Ethics committee (Studio RICe, 14591_oss CEAVC Studio RICe, 14591_oss and subsequent amendments). Other information on the RICe study is reported elsewhere [23]. All patients signed a written informed consent before starting treatment with rimegepant.

The online open database Research Electronic Data Capture (REDCap) and the *Empedocle* electronic

platform (developed for the RICe study) has been used for data collection.

At the time of the study, rimegepant was not subsidized by the Italian national health service. Therefore, patients either received the drug with no cost from clinical centers (by drug sampling from the company, which was independent from the GAINER study) or paid for it.

Inclusion criteria were: i) individuals aged 18 years or older, ii) diagnosis of migraine without aura, migraine with aura, or chronic migraine (CM) according to ICHD-3([24]); ii) at least 3 monthly migraine days (MMDs) in the 3 months before enrollment; iii) a good compliance to study procedures; iv) availability of headache diaries of least one month before enrollment.

Exclusion criteria: i) subjects with any contraindications to gepants; ii) concomitant diagnosis of medical diseases and/or comorbidities that could undermine the study according to clinicians; iii) pregnancy and breastfeeding.

Participants were enrolled regardless of the number of preventive treatments interrupted for lack of efficacy (no meaningful improvement in the frequency of headaches after the administration of drugs for ≥ 3 months at appropriate dose) or not tolerated, including onabotulinumtoxin-A and anti-CGRP monoclonal antibodies (mAbs).

Before rimegepant intake, clinicians verified and collected headache diagnosis, clinical and demographic features (including accompanying symptoms, duration and severity of the attack, preventive treatments, monthly headache days [MHDs]), MMDs, number of acute drugs per month, and days with at least one acute drug intake per month. Previous or current use of triptans and self-reported effectiveness were also collected. Finally, the Headache Impact Test (HIT-6) [25] and the MIDAS [26] questionnaires were collected. A headache day was defined as any day on which a patient recorded any type of headache, a MMD was defined as any day of headache with the characteristics of migraine or use of triptans [24]. For this study, a month was defined as 30 days.

Study participants were instructed to treat a migraine attack with rimegepant 75 mg ODT as first acute migraine treatment. In line with our real-world design, patients were allowed to take rimegepant according to their preference, namely at any time from pain onset and regardless of pain severity.

Before rimegepant intake, participants reported the following data on a dedicated eDiary: timing of headache onset, timing of rimegepant intake, intensity of pain at rimegepant intake (0 to 3 Likert scale [0 = none, 1 = mild, 2 = moderate, 3 = severe]), disability (through four-point scale of the Functional Disability Scale [FDS]), accompanying symptoms, most bothersome symptom (MBS) with related intensity. After rimegepant intake, they collected the same variables at 30, 60, 90 and 120 (2 h) minutes (Fig. 1). Participants were allowed to take a rescue medication, based on their preference, only after 120 min from rimegepant intake. Participants were also requested to record their symptoms in the eDiary 24 h post-dosing.

Adverse events (AEs) and subjective tolerability (from very bad to excellent) were collected. Participants were also asked to report a subjective comparison with triptans (if used) and a global evaluation of rimegepant (0–10 scale). Finally, evaluation on the acute treatment was assessed through the Assessment of Current Therapy Questionnaire (Migraine-ACT) [27].

Outcomes and analysis

According to the guidelines of the International Headache Society, the primary outcome of GAINER study was to evaluate rimegepant effectiveness through the assessment of: pain freedom at 2 h post dose during the first attack (reported as 0 on a 4-point Likert scale [0 = none, 1 = mild, 2 = moderate, 3 = severe]). We associated the assessment of the occurrence of treatment emergent side effects (TEAEs) during the 24 h after the first administration, to evaluate for the first time the safety of the drug in a real-world population.

Secondary outcomes included: i) pain relief at 2 h post dose (identified as no pain or decrease in pain from moderate-severe to mild at 2 h after treatment and before taking any rescue medication); ii) ability to function normally at 2 h post dose (through four-point scale of the Functional Disability Scale [FDS]); iii) freedom from the MBS at 2 h post dose; iv) rescue medications use; v) pain freedom at 24 h, defined as the percentage of patients who were pain-free at the 24 h follow up without the intake of a rescue medication; vi) no-pain relapse between 2 and 24 h, defined as the percentage of patients who were pain-free at the 24 h follow up in the subset of participants with pain freedom at 2 h post-dose and without the intake of a rescue medication; vii) treatment satisfaction (from 0 to 10); viii) self-reported treatment effectiveness (Migraine-ACT).

Statistical analysis

Due to lack of data regarding gepants effects in the real-world setting, we did not perform a structured sample size calculation. Based on our clinical and research experience, we predetermined that enrollment of at least 100 subjects would be representative of the outpatient clinic population attending our headache centers and sufficient to perform a statistical analysis. Normality test by means of the Shapiro–Wilk test proved the non-normality of several variables. Thus, statistical analysis was conducted with non-parametric tests. We reported mean [95 confidence interval] for continuous variables and

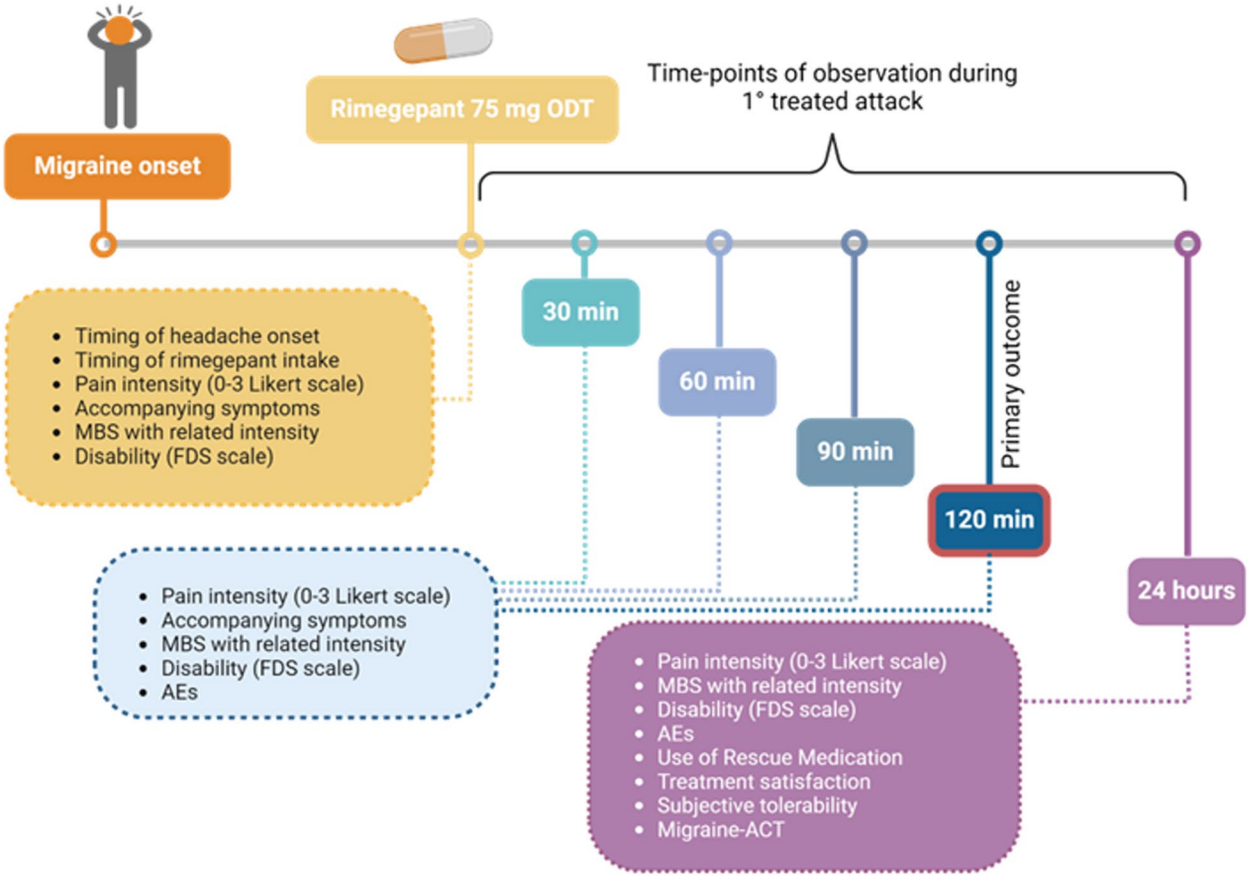

Fig. 1 Study design. Legend: AEs, adverse events; ODT, oral disintegrating tablet; MBS, most bothersome symptom; FDS, Functional Disability Scale. Rescue medications were allowed after 120 min from rimegepant intake; Migraine-ACT, Assessment of Current Therapy Questionnaire. Created with BioRender.com

number (percentage) for categorical data. No imputation was done for missing data. Univariate analyses were performed with Mann–Whitney or Kruskal–Wallis tests for independent groups comparison, and chi-square test for categorical variables. Cochran Q test was adopted to assess significant modification of pain freedom over time. The analysis was completed with a logistic regression to assess which variables were independently associated with 2 h pain freedom, after correction for age and sex.

A two tailed p-value < 0.05 was considered significant for all variables, with a Bonferroni's correction where appropriate. All data were analyzed using SPSS software version 26.0 (IBM Corp. SPSS Statistics, Armonk, NY, USA) and graphs designed using GraphPad Prism version 9.00 (La Jolla, USA).

Results

Study population

The final study population included 103 participants (74.8% female, age 44.4 [42.0—46.7] years, disease duration 27.5 [24.8 – 30.2] years). Seventy-eight (75.7%) participants had episodic migraine (EM), while 25 (24.3%) had CM. Among CM participants, 11 (44.0%) had a concomitant diagnosis of medication overuse headache. The average number of previously failed preventive classes was 2.7 [2.3 – 3.2], with 65% ($n = 67$) of participants taking a preventive treatment at baseline (stable over the previous three months in 42.7% of cases). Thirty-six participants (34.9%) had at least one comorbidity.

At baseline, participants presented a mean of 9.6 [8.2 – 10.9] MMDs with untreated attacks lasting 31.2 [26.2 – 36.2] hours. They reported a mean of 8.7 [7.2 – 10.3] days of acute drug intake per month and 13.3 [10.8 – 15.8] doses of acute medications per month. Clinical and demographic features are fully detailed in Table 1.

Eighty-seven participants (84.5%) declared a current or previous use of triptans, with a subjectively reported good/very good effectiveness in 42.7% of cases, a poor effectiveness in 40.0% and no effectiveness in 17.3% of cases (Supplementary Table 2).

Table 1 Clinical and demographic features of study population

	TOT	EM	CM	*p*-value
n	**103**	**78**	**25**	-
Age (years)	44.4 [42.0 - 46.7]	43.6 [41.1 – 46.0]	46.8 [40.8 - 52.8]	0.214
Female (%)	77 (74.8%)	62 (79.5%)	15 (60.0%)	0.065
Aura (%)	15 (14.6%)	11 (14.1%)	4 (16.0%)	0.755
Medication overuse (%)	11 (10.7%)	-	11 (44.0%)	-
Disease duration (years)	27.5 [24.8 – 30.2]	27.0 [24.1 – 29.9]	28.7 [22.0 – 35.3]	0.630
Duration of chronic migraine (years)	-	-	17.8 [12.3 – 23.4]	-
MHDs	11.7 [10.1 – 13.3]	7.8 [7.0 – 8.5]	23.9 [21.2 – 26.6]	**0.001**
MMDs	9.6 [8.2 – 10.9]	6.8 [6.1 – 7.5]	18.2 [14.8 – 21.5]	**0.001**
Days of acute drug intake/ month	8.7 [7.1 – 10.3]	6.3 [5.3 – 7.3]	16.4 [12.1 – 20.7]	**0.009**
Doses of acute drugs/month	13.3 [10.8 – 15.8]	10.3 [8.6 – 12.0]	22.1 [14.5 – 29.7]	**0.001**
Duration of migraine attack (hours)	31.2 [26.2 – 36.2]	30.9 [25.0 – 36.7]	32.0 [21.3 – 42.8]	0.866
MIDAS (*n*=91)	43.6 [34.4 – 52.9]	30.9 [24.9 – 37.1]	83.5 [55.0 – 111.9]	**0.001**
HIT-6 (*n*=46)	54.8 [49.2 – 60.5]	55.5 [49.4 – 61.6]	53.3 [39.7 – 66.8]	0.298
Previously failed preventive treatments				
Classes of preventive treatment	2.7 [2.3 – 3.2]	2.7 [2.2 – 3.2]	2.9 [2.0 – 3.8]	0.861
Anti-CGRP mAbs	2 (1.9%)	0 (0.0%)	2 (8.0%)	0.057
BoNT-A	13 (12.6%)	9 (11.5%)	4 (16.0%)	0.512
Ongoing preventive treatments				
Ongoing preventive treatment	67 (65.0%)	47 (60.3%)	20 (80.0%)	0.093
Anticonvulsants	6 (5.8%)	2 (2.6%)	4 (16.0%)	**0.030**
B-blockers	9 (8.7%)	8 (10.3%)	1 (4.0%)	0.449
Calcium channels blockers	1 (1.0%)	0 (0.0%)	1 (4.0%)	0.243
Sartans	2 (1.9%)	0 (0.0%)	2 (8.0%)	0.057
SSRI	4 (3.9%)	3 (3.8%)	1 (4.0%)	1.000
SNRI	3 (2.9%)	3 (3.8%)	0 (0.0%)	1.000
Tricyclic antidepressants	15 (14.6%)	10 (12.8%)	5 (20.0%)	0.514
BoNT-A	12 (11.7%)	7 (9.0%)	5 (20.0%)	0.158
Anti-CGRP mAbs	28 (27.2%)	21 (26.9%)	7 (28.0%)	1.000

Values in bold are statistically significant

Legend: *CGRP* calcitonin gene related peptide, *mAbs* monoclonal antibodies, *BoNT-A* onabotulinumtoxin-A, *SSRI* selective serotonin reuptake inhibitors, *SNRI* serotonin-norepinephrine reuptake inhibitors, *MHDs* monthly headache days, *MMDs* monthly migraine days, *EM* episodic migraine, *CM* chronic migraine

Rimegepant was prescribed for one or more of the following reasons: lack of effectiveness (69.9%), as an alternative (45.7%), or for adverse events / lack of tolerability (13.6%) of the usual acute treatment.

Baseline clinical features of migraine attack treated with rimegepant

Participants reported rimegepant intake after a mean of 63.6 [49.9 – 77.4] minutes from headache pain onset. Seventy-one (68.9%) subjects took rimegepant within one hour from headache onset. At the time of intake, they rated pain intensity as severe in 40.8% of cases, while the disability was moderate/severe in 50.5% of cases. Most of participants (90%) reported associated symptoms, mainly photophobia (71.8%), phonophobia (62.1%) and nausea (57.3%). The MBS was reported as moderate-severe in 71.4% of individuals, with nausea as the most prevalent (47.5%). Baseline clinical features of the treated migraine attack are detailed in Table 2.

Table 2 Baseline clinical features of treated migraine attack

	TOT	EM	CM	*p*-value
n	**103**	**78**	**25**	-
Pain intensity				
Mild	6 (5.8%)	6 (7.7%)	0 (0.0%)	**0.017**
Moderate	55 (53.4%)	46 (59.0%)	9 (36.0%)	
Severe	42 (40.8%)	26 (33.3%)	16 (64.0%)	
Timing of rimegepant intake (minutes)				
Total attacks	63.7 [49.9-77.4]	64.7 [48.2-81.1]	60.6 [34.4-86.8]	0.530
Disability level				
None	4 (3.9%)	3 (3.8%)	1 (4.0%)	0.930
Mild	32 (31.1%)	25 (32.1%)	7 (28.0%)	
Moderate/severe	52 (50.5%)	38 (48.7%)	14 (56.0)	
Complete	15 (14.6%)	12 (15.4%)	3 (12.0%)	
Associated symptoms				
Photophobia	74 (71.8%)	57 (73.1%)	17 (68.0%)	0.618
Phonophobia	64 (62.1%)	50 (64.1%)	14 (56.0%)	0.486
Nausea	59 (57.3%)	42 (53.8%)	17 (68.0%)	0.251
Vomiting	6 (5.8%)	3 (3.8%)	3 (12.0%)	0.152
None	10 (9.7%)	7 (9.0%)	3 (12.0%)	0.702
Most bothersome symptom (*n*=99)				
Photophobia	28 (28.3%)	22 (28.9%)	6 (26.1%)	0.167
Phonophobia	23 (23.2%)	21 (27.2%)	2 (8.7%)	
Nausea	47 (47.5%)	32 (42.1%)	15 (65.2%)	
Vomiting	1 (1.0%)	1 (1.3%)	0 (0.0%)	
Most bothersome symptom severity at baseline (*n*=98)				
None	10 (10.2%)	7 (9.3%)	3 (13.3%)	0.825
Mild	18 (18.4%)	13 (17.3%)	15 (65.2%)	
Moderate/severe	70 (71.4%)	55 (73.4%)	3 (12.5%)	

Values in bold are statistically significant. The number of patients included in the subgroup are reported

Legend: *EM* episodic migraine, *CM* chronic migraine

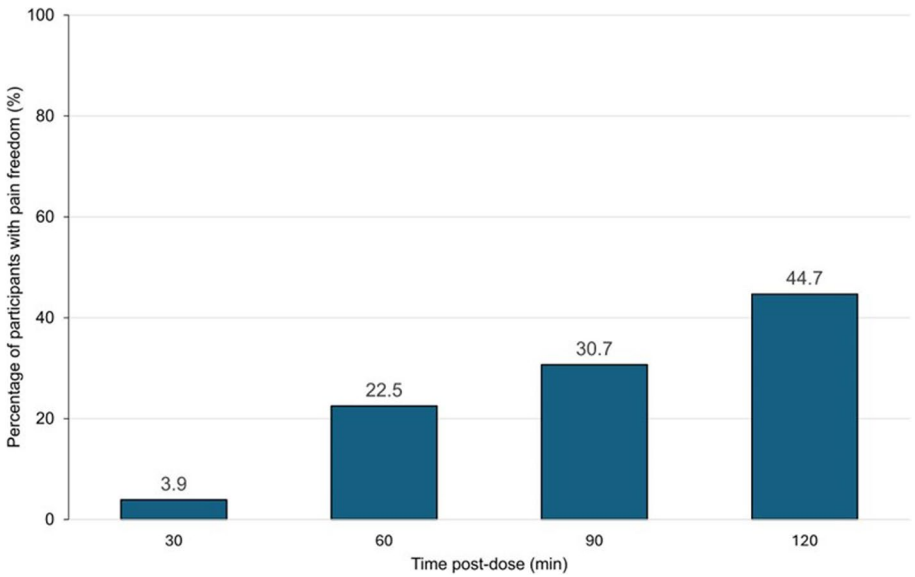

Fig. 2 Pain freedom within 120 min (2 h) from rimegepant intake

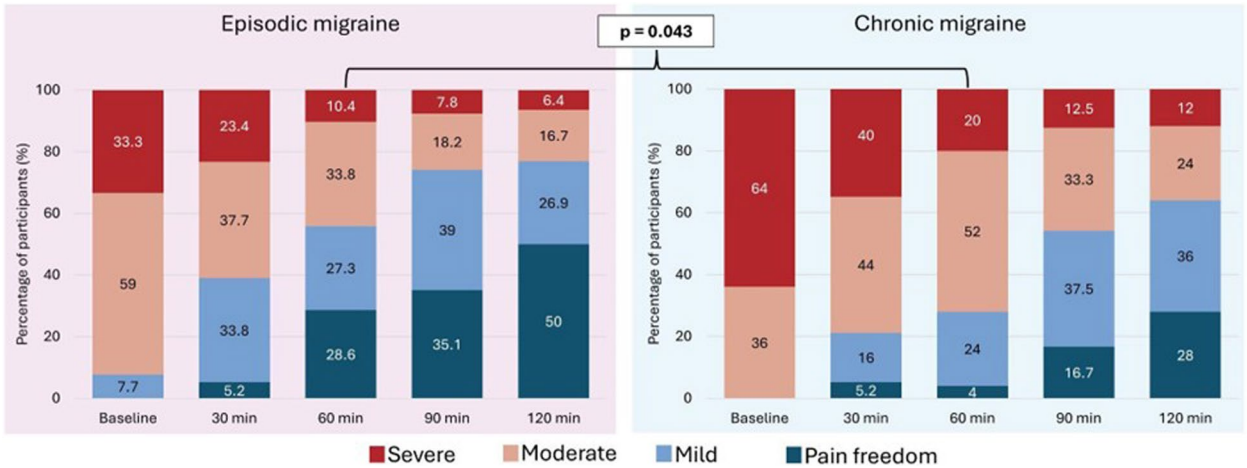

Fig. 3 Pain intensity trend within 120 min (2 h) from rimegepant intake in episodic and chronic migraine groups

Primary effectiveness outcome – pain freedom at 2 h post rimegepant intake

The percentage of participants reporting pain freedom 2 h post dose was 44.7% (46/103), 50% for EM and 28% for CM ($p=0.144$) Figs. 2 and 3. The rate of pain freedom after rimegepant intake gradually increased every 30 min, up to 2 h post dose ($p<0.001$ – Fig. 2). At 60 min from rimegepant intake, the rate of pain freedom was higher in the EM group (28.6%) compared to the CM group (4.0%) ($p=0.043$). This difference was not significant at 30 and 90 min after rimegepant intake (Fig. 3).

Pain freedom 2 h post dose was not influenced by pain intensity at baseline ($p=0.316$). Conversely, it was associated with the timing of intake ($p=0.032$); in particular, we found a higher rate of 2 h pain freedom when rimegepant was taken within 1 h from pain onset (80.4%) (Fig. 4). The timing of intake from pain onset was 52.7 [30.8–74.6] minutes in individuals who achieved pain freedom 2 h post dose, and 72.6 [54.9–90.4] minutes for individuals who did not achieve pain freedom 2 h post dose ($p=0.007$).

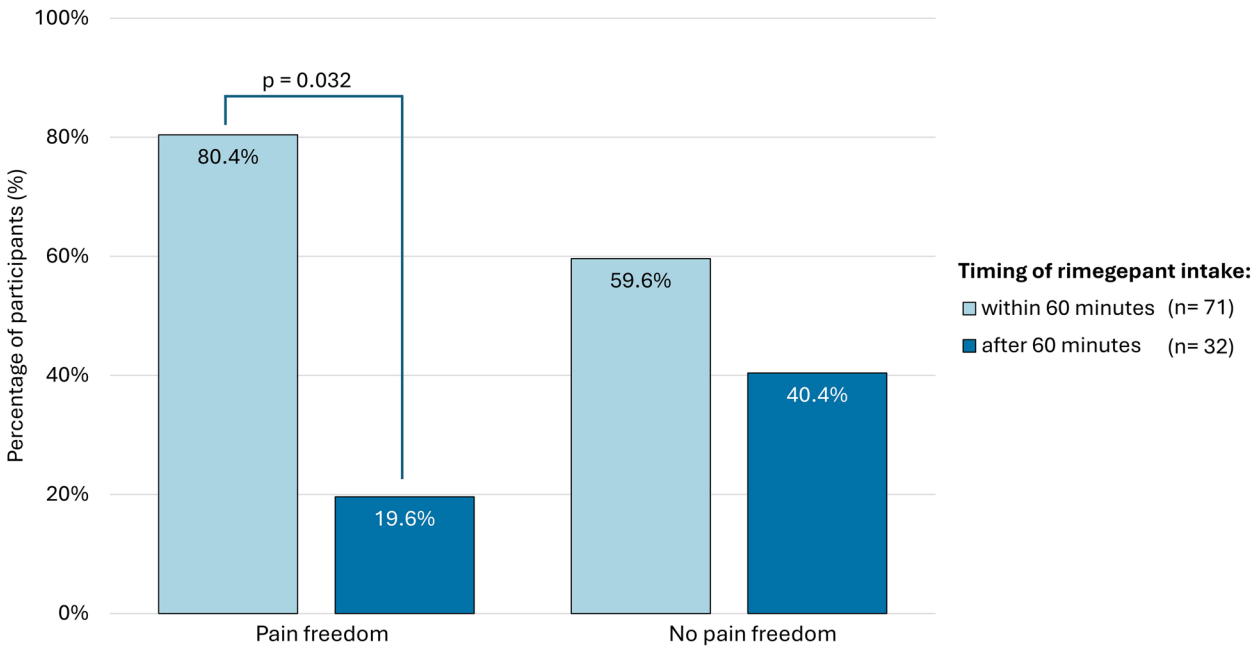

Fig. 4 Clinical outcome 120 min (2 h) post-dose according to the timing of rimegepant intake

Pain freedom 2 h post dose was associated with a lower number of previously failed preventive classes ($p=0.037$), lower MHDs ($p=0.015$) and lower MMDs ($p=0.042$).

According to a logistic regression analysis, after correction for age and sex, the only factor independently associated with 2 h pain freedom was the number of MHDs ($p=0.033$, Exp(B)=0.921). The Hosmer–Lemeshow test showed a proper good-of-fit ($p=0.626$). This model explained up to 21.2% (Nagelkerke R^2) of variability.

Secondary effectiveness outcomes

Pain relief at 2 h, freedom from the most bothersome symptoms, and migraine-related disability

Pain relief 2 h post dose, was achieved by 70.9% of participants (73/103). Pain relief 2 h post dose was neither influenced by baseline pain severity ($p=0.060$) nor by the timing of rimegepant intake (within 60 min vs. more than 60 min; $p=0.881$). The mean timing of intake from pain onset was 61.9 [46.1–77.8] minutes in individuals who achieved pain relief 2 h post dose, and 67.9 [39.0–96.7] minutes for individuals who did not achieve pain relief 2 h post dose ($p=0.557$).

Freedom from the most bothersome symptom was reported in 56.3% of cases. Complete recovery from migraine related disability 2 h after rimegepant intake was achieved by 47.6% of individuals (Supplementary Table 3).

Migraine related disability 2 h post dose was not associated with the timing of rimegepant intake ($p=0.830$). Conversely, it was influenced by baseline pain intensity, with a persistent higher disability reported by individuals with severe pain at the time of rimegepant intake ($p=0.035$).

Response at 24 h

Twenty participants (19.4%) took a rescue medication in the timeframe 2 h - 24 h post dose. Specifically, 10.7% took NSAIDs, 5.8% triptans, 5.8% combination analgesics, and 1.9% acetaminophen. Pain freedom at 24 h (including patients without the intake of a rescue medication) after rimegepant dose was 64.1% ($n=66$). Forty-one subjects (39.8%) reported no-pain relapse in the timeframe 2 h - 24 h post dose. Associated symptoms were absent in 71 participants (68.9%).

Patient' reported outcomes (PROs)

Regarding rimegepant intake, participants reported a global satisfaction of 7.1 [6.6 – 7.6] on a 0–10 scale. Migraine Assessment of Current Therapy Questionnaire (ACT) for rimegepant was higher compared to the usual acute drug ($p=0.001$), without differences between EM or CM groups ($p=0.246$).

Data regarding triptan effectiveness was available for 75 individuals out of 87 subjects who has ever used triptans. Triptan response was rated as good/very good by 32 individuals (42.7%) and absent/poor by 43 (57.3%). Rimegepant 2 h pain freedom was not associated with triptan response (2 h pain freedom in triptan responders: 40.6% *vs.* triptan non-responders: 59.4%, $p=0.816$).

Among the 87 participants who previously used triptans, the experience with rimegepant was considered better than triptans in 48.3% of cases (42/87), comparable to triptans in 24.1% of cases (21/87), and worse than triptans in 27.6% (24/87). Reasons for rimegepant preference over triptans were: complete effectiveness (45.2%), higher effectiveness (42.9%), faster action (26.2%), and/or higher effectiveness on associated symptoms (19%). Notably, rimegepant preference over triptans was higher among individuals with episodic migraine (EM: 52.9% *vs.* CM: 31.6%; $p=0.027$).

Tolerability and adverse events analysis

At least one adverse event was reported in 15.5% of cases (16/103). Only 5 subjects reported more than one adverse event. All adverse events were mild, and self-limiting. The most common adverse events (>2%) were fatigue (5.8%, $n=6$), gastrointestinal symptoms (5.8%, $n=6$), somnolence (3.9%, $n=4$), and transient cognitive difficulties (2.9%, $n=3$). The overall rimegepant tolerability was rated as good/excellent by 88 participants (85.4%).

Discussion

In the present study we detail the effectiveness and tolerability of rimegepant in the management of the first-treated migraine attack in a real-world setting.

Our findings may be summarized as follow: i) 2 h after rimegepant intake, 44.7% and 82.7% of participants achieved complete pain freedom or pain relief, respectively; ii) complete freedom from the MBS 2 h post dose was reported by 56.3% of participants; iii) only 19.4% of participants needed a rescue medication, with a percentage of pain freedom at the 24 h follow-up of 64.1%, and a percentage of no-pain relapse in the timeframe 2 h - 24 h post dose of 39.8%; iv) adverse events were present in 15.5% of participants, predominantly fatigue, gastrointestinal symptoms, somnolence, and transient cognitive difficulties.

Our data largely supports the effectiveness, safety and tolerability of rimegepant for the acute treatment of migraine in a real-world setting. The proportion of subjects with a positive therapeutic response was higher than those reported in RCTs and their open-label extensions [19–21]. In RCTs, the rate of pain freedom 2 h post dose ranged from 19 to 21% (vs. 11 to 14% in placebo group). This discrepancy between real-life studies and RCTs has

already been noted looking at preventive findings with monoclonal antibodies targeting the CGRP pathway and could be partly explained by the different population enrolled as well as by the possible placebo effect related to the uncontrolled study design [13, 16].

In particular, our population included individuals characterized by a high-frequency episodic migraine pattern (with an average of 10 MMDs), a CM diagnosis in 25% of subjects, 44% of them with concomitant medication overuse headache, and the high number of prior preventive treatment failures. By contrast, rimegepant trials for acute treatment included only EM participants with relatively low frequency, namely less than five MMDs [19, 21, 28]. In addition, no RCTs were conducted in CM. Thus, GAINER is the first study to report data for rimegepant for the acute treatment in CM. Despite the baseline features reported above for our cohort, which includes a large component of difficult-to-treat" subjects, we found a high response rate to rimegepant as an acute migraine treatment, corroborating the clinical usefulness of this treatment. Another difference is represented by the baseline pain severity. In RCTs, participants were instructed to treat the attack when pain was moderate-severe, while in our study, the subjects were allowed to treat a migraine attack of any intensity. So said, only 5.8% of migraine attacks were of mild intensity at rimegepant intake, thus it is difficult to hypothesize that this methodological difference may account for this discrepancy.

Although the comparison between EM and CM was not the primary objective of our study, our data highlighted differences according to participants migraine frequency and baseline diagnosis. Indeed, migraine frequency was the only factor associated with the effectiveness of rimegepant, with a slightly lower effectiveness in patients with CM compared with those with EM and a slower onset of action in the CM group. Notably, other patients' features, such as age and sex, were not associated with treatment response. These findings are worthy of confirmation in larger and specifically designed studies and might signal a difference between the pathophysiology of EM and that of CM. Patients with CM might have accumulated mechanisms favoring resistance to acute treatments via sensitization to pain [29–31]. The preliminary demonstration of rimegepant effectiveness in CM is of the utmost interest. CM subjects have more frequent attacks and are forced to take an elevated number of acute drugs with a consequent high risk of medication overuse [10]. Preclinical data in the animal migraine model suggests that gepants are not associated with an increased risk of central sensitization [32]. From a clinical perspective, a long-term open-label extension described how the acute use of rimegepant in subjects with at least 6 MMDs determined a concomitant reduction of migraine frequency across a 1-year follow-up period [33].

According to our data, pain freedom with rimegepant was associated with timing of intake, with higher chances of obtaining pain freedom 2 h post dose when taking rimegepant within 1 h from pain onset. This is in line with data on acute migraine treatment, including triptans, for which early intake was associated with a better effectiveness [34]. Conversely, we did not find an association between the timing of rimegepant intake and pain relief. Therefore, our data supports that the late intake of rimegepant could still provide a certain degree of effect, although the relief may be partial in those cases. This finding is relevant when discussing therapeutic options with patients in clinical practice.

Notably, both pain freedom and pain relief were not dependent on pain intensity at baseline, suggesting rimegepant versatility in different spectra of migraine intensity.

The relief from the most bothersome symptom was in line with other effectiveness outcomes, confirming a positive role of rimegepant in symptoms other than pain, as well.

Another relevant finding of our study was that 64% of participants treated with rimegepant were pain-free at 24 h without a rescue medication. The percentage of participants without pain relapse in the 2 h - 24 h timeframe was 39.8%. As comparator for this last figure, randomized data on triptans showed that 24 h sustained pain-free response was not superior to 54.1% and lower than 30% in most cases [6]. Our data suggests rimegepant as a good option for long-lasting migraine attacks. This finding should be interpreted with caution, bearing in mind the open-label nature of our study.

Safety assessment and patient-reported outcomes supported a good tolerability and subjective satisfaction. The high satisfaction of patients was likely led by excellent tolerability together with effectiveness. In about half of cases, patients reported that their experience with rimegepant was even better than that with triptans. Our data are in line with randomized data showing that the efficacy of gepants was independent from previous response to triptans and confirms that gepants could be a good option for those individuals not responding to triptans [20, 35].

To the best of our knowledge, GAINER is the first study reporting the effectiveness of rimegepant in the acute treatment of migraine in the real-world setting. The strengths of the GAINER study include its prospective and multicentric design, reflecting the common clinical practice of several Italian headache centers, and the link to a nationwide registry of patients with headache

disorders. Prospective data collection up to 24 h post dose is another strength of the study. Furthermore, the study adheres to guidelines for trials of acute treatment of migraine attacks in adults and was pre-registered.

This study has limitations as regards the absence of a pre-specified sample size and the lack of a placebo control group. Further work is needed to confirm these findings. We also based our findings on self-reported data collection. Although we adopted an ad-hoc specific diary and we delivered a thorough training to participants, we cannot completely rule out a certain degree of reporting biases. We must also acknowledge that we did not properly collect some information at baseline, specifically regarding migraine comorbidities. Indeed, in the present study the presence of possible co-existent diseases appears to be under-reported. This does not allow for an in-depth description of rimegepant effectiveness and tolerability in subjects with cardio-vascular or psychological comorbidities. Finally, in the absence of reimbursement criteria, rimegepant was prescribed only to outpatients of headache centers who received the drug with no costs or had to pay for it, potentially leading to a selection bias of a more difficult-to-treat population.

Conclusion

Our data on an Italian cohort of subjects with either EM or CM assessed in the real-world setting supports the effectiveness and tolerability of rimegepant for the acute treatment of migraine. The rate of 2 h pain freedom was 44.7%, being numerically higher in the EM group (50%) compared to the CM group (28%). Adverse events were reported by 15.5% of participants, mild in intensity and self-limiting.

Supplementary Information

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Supplementary Material 1.

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Figure 1 is created with Biorender.com.

Italian Headache Registry (RICe) Study Group: Davide Mascarella[10], Matteo Bolchini[7], Gennaro Saporito[6], Licia Grazzi[8], Andrea Marcinnò[18], Gabriele Garascia[17], Enrico Grassi[12], Catello Vollono[13], Francesca Boscain[11], Martino Gentile[9], Andrea Burgalassi[1], Federico De Santis[19], Michele Corrado[2,3], Grazia Sances[3], Cristina Tassorelli[2,3], Maria Albanese[20], Michele Trimboli[21], Alberto Doretti[22]. This work has been supported by Regione Lombardia within the PERLA project.

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Code

The study was preregistered on clinicaltrial.gov, NCT05903027.

Authors' contributions

RDI, GV, GS and LFI had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; designed the study; drafted the manuscript. RDI and GV performed statistical analysis. GS, MR, EP, CF and FC performed administrative and technical support. All Authors recruited patients, and critically reviewed the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Data availability

Data supporting the findings in the present study are reported in the article and in the supplementary materials. The data collected and analyzed for the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved as a part of the *Registro Italiano Cefalee (RICe)* study by the local Ethics Committee (CEAVC Studio RICe, 14591_oss and subsequent amendments 2022–609; 2023).

Competing interests

LFI received fees and Honoraria for advisory boards, speaker panels from Teva, Eli Lilly, Lundbeck, Pfizer and AbbVie. GV received personal fees from Lundbeck; M.S has received speaker honoraria from Novartis, Teva, and Lilly; AR has received speaker honoraria from Allergan, Lilly, Novartis, Biogen, and Teva and serves as an associate editor of Frontiers in Neurology (Headache Medicine and Facial Pain session); SC received honoraria for speaker panels from Teva and Novartis; MPP received speaker honoraria and advisory board participation from Abbvie, Idorsia, Eli-Lilly, Novartis, Pfizer, TEVA; RO reports personal fees and non-financial support from Allergan-AbbVie, Eli Lilly, Novartis, Pfizer, and Teva; RDI reports personal fees and non-financial support from Eli-Lilly, AbbVie, Pfizer, Lundbeck, and TEVA. Other authors have no conflicting interests on this specific study.

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