Mab-Mig: Registry of the Spanish Neurological Society of Erenumab for Migraine Prevention. Three-Months Results

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Abstract

Background Erenumab was approved in Europe for migraine prevention in patients with ≥4 monthly migraine days (MMD). In Spain, Novartis started a personalized managed access program which allowed free access to erenumab before official reimbursement. The Headache Study Group of the Spanish Neurological Society started a registry to monitor real-world safety and efficacy, and all Spanish headache experts were invited to participate. Methods Patients fulfilled ICHD3 criteria for migraine and had ≥ 4MMD. Sociodemographic and clinical data were registered as well as MMD, headache frequency (MHD), prior and concomitant preventive treatment, medication overuse headache (MOH), migraine evolution, adverse events, and PROs: HIT6, MIDAS, and PGIC. A >50% reduction of MMD after 3 months was considered as response. Results We included 210 patients (female 86.7%, mean age 46.4 years old) from 22 hospitals from February 2019 – to – June 2020. Most patients (89.5%) suffered from chronic migraine with a mean evolution of 8.6 years. MOH was present in 70% of patients, and 17.1% had migraine with aura. Average of prior preventive treatment failure was >7 (BoNT/A had been used by 95.2%). Most patients (67,6%) started with erenumab 70mg. 61% of patients were also taking oral preventive drugs or getting simultaneous BoNT/A (27.6%). Responder rate was 37.1% and the mean reduction of MMD was -6.28 and MHD: -8.6. Regarding PROs: MIDAS: -35 p., HIT6: -11.6 p., PIGC: 4.7 p. Predictors of good response were: HIT6 score (p =0.01), prior preventive treatment failures (p =0.026), absence of MOH (p =0.039), and simultaneous BoNT/A treatment (p <0.001). 20% had adverse event, but only two of them were severe (0.9%) which led to treatment discontinuation. Mild constipation was the most frequent adverse event (8.1%). Conclusion In real-life, in a personalized managed access program, erenumab shows a good profile of efficacy and an excellent safety in migraine prevention in our cohort of refractory patients.

Background

Migraine is the second among the world´s leading neurological causes of disability and first among young women, according to the GBD2019[1]; and approximately 38% of migraine patients[2] need a preventive treatment to reduce this disability. In Spain, several first line preventive drugs for episodic migraine are available: topiramate, sodium valproate, amitriptyline, flunarizine and beta-blockers; while only botulinum toxin type A (BoNT/A) and topiramate are for chronic migraine[3]. The number of migraine days per month (MMD) after 12 weeks of treatment is the main variable of efficacy for a preventive drug in migraine[4], despite the known decrease in prevention adherence beyond 12 weeks[5,6,7]. The loss of efficacy and side effects account for this progressive decrease of adherence. For these reasons, we urgently needed new preventive drugs, and anti-CGRP monoclonal antibodies (CGRP MABs) have arrived to cover these needs.CGRP is a neuropeptide distributed throughout the human body and highly concentrated in the trigeminovascular system[8]. The levels of CGRP are increased during the migraine attack in blood, tears, saliva, and cerebrospinal fluid, and normalized after the attack[9,10]. They are also increased in chronic migraine (CM)[11]. Moreover, the intravenous administration of CGRP provokes migraine-like headaches in migraine patients and voluntaries[12]. Therefore, CGRP is an excellent target in

the migraine therapy.At present, there are three marketed subcutaneous GCRP MABs in Spain: erenumab (Aimovig®), galcanezumab (Emgality®), and fremanezumab (Ajovy®). CGRP MABs block the CGRP-receptor (erenumab) or the CGRP-ligand (galcanezumab, and fremanezumab). Phase II[13-18] and phase III[19-33] trials against placebo have shown an excellent profile of safety and efficacy of CGRP MABs in migraine prevention. Additionally, several meta-analyses have countersigned their results[34-39]. As conclusion[39], no significant difference between each CGRP MAB and placebo groups has been shown, and all efficacy variables were significantly better for CGRP MABS compared to placebo. Finally, similar efficacy results were separately obtained for erenumab, fremanezumab, and galcanezumab.Erenumab was the first CGRP MAB approved in Europe. The European Medicines Agency approval was communicated the 26th of July 2018, and the Spanish Medicines Agency and Medical Devices authorized a personalized managed access program which allowed neurologists to treat patients before official reimbursement in January 2019. In the same date the Headache Study Group of the Spanish Neurological Society (GECSEN) started MAB-MIG. This is an, independent and multicentre, registry of patients with migraine treatment with CGRP MABs promoted by GECSEN. We created MAB-MIG to monitoring real-world safety and efficacy, inviting headache specialists around the country. We present the real-world evidence concerning safety and efficacy of the first 210 migraine Spanish patients after 12 weeks treatment with erenumab.

Methods

MAB-MIG is a prospective post-approval registry of CGRP MABs, and the GECSEN board (R. Belvís, S. Santos, G. Latorre and C. Gonzalez-Oria) constitutes its scientific committee, plus two independent members (P. Pozo-Rosich and R. Leira) as advisors. This committee selected the variables and advised the design of the database. It also resolved queries of the investigators and assessed the final database and the statistical analyses. Each researcher acted according to their clinical criteria. The recommendations on erenumab treatment in migraine, proposed by international experts[40-42], were made available to researchers; but the committee made no further clinical recommendationsAll patients included fulfilled the International Headache Society criteria for migraine[42]. Patients were older than 18 years old and younger than 65 years old. They had at least 4 MMD for the last three months and were treated with erenumab during a minimum 12-week period. The onset of migraine was before age 50 and they had the diagnosis of migraine for a minimum one year before the inclusion in the registry. Patients with cardiovascular pathology were excluded**.**Patients were included in the MAB-MIG registry between February 2019 and June 2020. All centres were anonymized and sent information regarding their patients in encrypted form.We collected the followed variables: 1. Demographical data; 2. Clinical data as migraine form (with/without aura), CM versus high frequency episodic migraine (HFEM), years with migraine since onset, years with CM and 3. Efficacy variables. The following variables were collected at baseline and after 12-weeks treatment with erenumab: number of MMD, number of headache days (MHD) and patient-reported outcome endpoints - PROs: headache impact test (HIT-6) score and the migraine disability assessment questionnaire (MIDAS) score. Finally, patients implemented a patient global impact changes (PGIC) scale for evaluate their satisfaction. According to the International

Headache Society guidelines of controlled trials in migraine[4], *number of MMD* was considered the primary end point. Response was considered when a reduction superior to 50% was observed between baseline number of migraine days and the number of migraine days after 12-weeks treatment with erenumab. Additionally, we collected other variables: prior preventives drugs taken, including BoNT/A, previous acute medication overuse, erenumab treatment alone or in combination with another preventive drug, initial erenumab doses, and if there was a change in the erenumab dose schedule after 12 weeks. Other changes measured were conversion from CM to episodic migraine, and medication overuse headache (MOH). Safety analyses. We collected all the adverse events, and the MAB-MIG scientific committee classified them as related or non-related to erenumab treatment. According to Good Clinical Practice guidelines, we classified adverse events as mild, moderate, or severe, and we collected the dropout rate. For statistical analysis we used the SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). Results were expressed as median and standard deviation or as absolute number and percentages. Patient data were classified into two groups: baseline visit and 12-week visit. Comparisons have been made using the Student's t-test for quantitative variables and contingency tables and the chi-square test for categorical variables. When the distribution of the data went out of normality, we used the Mann-Whitney U test. Statistical significance was considered when $P < 0.05$.Erenumab was approved as personalized managed access program which allowed free access to erenumab before official reimbursement in Spain in January 2019. Before applying to the Spanish Medicines Agency and Medical Devices, a prior approval from the Hospital Direction and Novartis was required.MAB-MIG was classified as a *low-intervention clinical trial* by the Spanish Medicines Agency and Medical Devices. Finally, MAB-MIG was approved by the Ethics Committee of Investigation with Medicines of the Health Area of Valladolid (PI 20-1790).

Results

We included 210 patients from 22 Spanish hospitals between February 2019-to-June 2020 who has finished at least 12 weeks of erenumab treatment. The included centres had a homogeneous geographic distribution around the country. The mean age was 46.4 years-old [18-65], and 86.7% of patients were women.

The mean migraine duration as disease in their lives was 26.5 years [3-to-25 years]. Most patients (89.5%) had CM with an evolution average for 8.6 years [3 months – to - 25 years] and the remain presented HFEM (10.5%). The 70% of patients presented MOH, and 17.1% fulfilled migraine with aura. The average of MMD was 17.1 days [4-30], and MHD was 23.5 days. The mean MIDAS score was 101.9 points, and the mean HIT-6 score was 68.8 points.

The average number preventive drugs that had previously failed was 7.8 [2-20] including BoNT/A. The later had been used by 95.2% of patients. The most frequently used oral preventive drugs were topiramate (98.2%), amitriptyline (98.2%), flunarizine (94.7%), and beta-blockers (92.9%).

The initial dose of erenumab was 70 mg in 67.6% of patients and 140 mg in the remain 32.4%.

Regarding simultaneous preventive treatments, only 39.5% patients received exclusively erenumab as preventive treatment**,** and in the remaining patients (60.5%) erenumab was added to another preventive drug: BoNT/A – 27.6%, topiramate - 12,2%, and miscellaneous drugs - 49.1%.

Regarding efficacy (Table 1), the responder rate was 37.1%, and the mean reduction of MMD was 6.5 days (from 17.1 to 11 days). MHD was also reduced in 8.6 days (from 23.5 to 14.9 days).

After the 12-week period of treatment (Figure 1), 28 patients (13.3%) discontinued the treatment. The reasons were: 1. Conversion into a low frequency episodic migraine (20 patients - 9.5%), 2. Lack of efficacy (4 patients – 1.9%), and 3. adverse events (4 patients - 1.9%).

The remaining 182 patients (86.7%) continued with erenumab treatment: with the same dose (44.7%), while 41,9% increased the dose thereafter (Figure 1). After three months of follow-up, 14.8% continued to receive simultaneously BoNT/A and 50% were still under treatment with oral preventive drugs.

Regarding PROs (Table 1): MIDAS score was reduced 35 points (from 101.9 – to - 66.9), HIT-6 reduced 11.6 points (from 68.8 to 57.2) and the mean PIGC assessment was 4.7 points.

The number of prior preventives was a predictor factors of good response (p=0.026) (Table 2). Specifically, 90% of responder patients had taken previously a mean of 5.9 preventive drugs, and patients who had taken nine or more preventive drugs account only 16% of the sample of responder patients. Furthermore, ineffectiveness prior to BoNT/A treatment does not predicted erenumab response (p=0.867). Other predictor factors were MIDAS score inferior to 100 points (p=0.006), less than 80 points in HIT-6 score (p=0.01), and absence of MOH (p=0.039). All the responder patients showed a HIT-6 score inferior to 80 points making this index in a strong predictor factor of response at this cut point.

None of both erenumab doses, 70 or 140 mg, showed a better statistical power as predictor of good response than the other (p=0.647). However, the simultaneous BoNT/A treatment showed the strongest predictor factor of a good response (p<0.001). On the contrary, simultaneous oral preventives did not predict a positive or negative response (p=0.213).

In addition, the presence of aura showed a non-significant tendency as a predictor factor of good response (p=0.088). However, age (p=0.557), gender (p=0.294), HFEM/CM (p=0.727), and evolution of CM (p=0.514) did not show any association to response.

The percentage of adverse events was 20%, but only four patients (1.9%), suffered severe adverse events provoking a treatment discontinuation. Two patients had a skin rash attributed to the first erenumab injection; the other two patients presented adverse events not related to erenumab: one patient, under paroxetine treatment, presented a serotoninergic syndrome while overusing zolmitriptan; and the other one was diagnosed of cutaneous melanoma, but the skin lesion existed previously to the erenumab treatment onset.

Specifically, forty-two patients presented 57 side-effects: being constipation the most frequent (7.6%). No patients needed treatment nor consultation by this adverse effect. Table 3 details adverse events reported by patients after 12 weeks of treatment with erenumab.

Finally, we did not find any predictive factor of adverse events. Only the dose of 140 mg showed a non-significant tendency to present more adverse events than the dose of 70 mg (p=0.069).

Discussion

We present the first multicentre and prospective Spanish real-world experience of erenumab in the preventive treatment of migraine. Erenumab presents an excellent safety profile in our registry, but a slightly lower efficacy (37% response) comparing to phase III clinical trials (39-50% response)[21-23,30].

This can be attributed to the fact that most of the 210 patients included were highly refractory chronic migraine patients. Most of patients of our study would have been excluded in clinical trials[19-32]. In a real-world clinical scenario, migraine patients who have exhausted all the therapeutic options are usually the first patients who receive a new marketed treatment. Another explanation could be that the more frequent erenumab initial doses prescribed was 70 mg because initial doses was a free decision of headache expert. Perhaps, efficacy could have been better if all the headache experts had started the treatment with the 140 mg doses. In this way, patients included in our study have a long history of migraine, a high number of MMD, and numerous failed preventive migraine drugs, with high impact in HIT-6 and MIDAS scales regarding research patients. Therefore, taking into account the degree of complexity of migraine in the patients in our study, an efficacy of 37% is better than it seems, despite of the better results of the erenumab phase III clinical trials[19-32], open-label extension studies[44-46], and meta-analysis[34-39].

As expected, the lower the scores on the HIT6 and MIDAS scales, and the fewer the number of preventive drugs that have previously failed, the more likely the erenumab treatment will be effective. These are the efficacy predictors that we have found in our study, together with the absence of MOH. Additionally, one unexpected predictive factor in our study has been the simultaneous treatment with erenumab and BoNT/A. This association was the strongest predictor factor of a good response and showed and excellent safety profile.

A huge number of real-world experiences analysing erenumab in migraine prevention are being published around the world[47-63], already including more than 2.000 patients with migraine. Among them, we can find eleven one-centre studies (seven prospectives[48,53,54,56,57,59,61] and four retrospectives[50,51,52,62]) and five multicentre (four prospectives[49,55,58,60] and one retrospective[63]). Our registry includes the second largest sample of migraine patients treated with erenumab in a multicentric prospective registry. A published Italian study[55] included more patients, 372 patients, but this initiative was composed by a group of headache experts and it included only ten Italian centres, and nine of them were localized in the north of Italy. Our study is the official registry of the Spanish Neurological Society and includes 22 centres with homogeneous representation of the country. Moreover, the average number of prior preventive drug

failures was 3-to-5 in the Italian study[55] and superior to 7 in ours, which means that our patients are more complex and treatment-refractory than the patients of the Italian study. Despite these differences, both the Italian study[55] and the other real-world experiences[47-63] conclude, like our registry, that erenumab is useful in the prevention of episodic and chronic migraine withs and presents an excellent safety profile.

Erenumab has shown scarce adverse events in our registry (20%), like the phase II[13-18] and III clinical trials[19-32], meta-analysis[34-39], open-label extension studies[44-46] and real-world experiences[46-62]. Most of the adverse events were mild and transient in our study. Mild constipation, flu-like symptoms, transient pruritus at the injection site and fatigue were the only adverse events with incidences superior to 2%. We only collected two severe adverse events related to erenumab treatment (two skin rash after injection) that represent 0.9% of our patients, a similar figure to that of clinical trials and real-world experiences (1-3%)[19-39,44-62].

Regarding the initial dose of erenumab, we have not found any difference on efficacy between them, unlike other studies[64]. On the other hand, the magnificent safety pattern of the two doses of erenumab is already known and our study confirms it, despite of the 140 mg dose showed a non-significant trend to present more adverse events than the dose of 70 mg.

This first reports of the results of the MAB-MIG registry have some limitations: First: patients included are the more refractories of Spanish headache units and they were waiting the arrival of MABs. For this reason, they do not exactly represent the Spanish real-world experience. Second: we present efficacy and safety results at three months of therapy, a short time of follow-up. Despite of these limitations, we would like to emphasize that our registry confirms the safety and efficacy of erenumab in the real-world clinical setting, providing two new insights: highly refractory migraine patients also respond after three months of treatment; and the concomitant use of BoNT/A and erenumab presents an excellent safety profile, as it has already been published in several studies[65-66].

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Declarations

Ethics approval and consent to participateMAB-MIG was classified as a *low-intervention clinical trial* by the Spanish Medicines Agency and Medical Devices, and was approved by the Ethics Committee of Investigation with Medicines of the Health Area of Valladolid, Spain (PI 20-1790).**Consent for publication**

Authors consent the publication of the paper MAB-MIG: REGISTRY OF THE SPANISH NEUROLOGICAL SOCIETY OF ERENUMAB FOR MIGRAINE PREVENTION. THREE-MONTHS RESULTS in The Journal of Headache and Pain.

Availability of data and materials All generated data in the MAB-MIG registry are not publicly available due to the Spanish law for the protection of personal data but are available from the corresponding author on reasonable request.**Competing interests**

Within the prior 24 months, RB, PI, PP-R, CG-O, and MSDR have received honoraria as consultant and/or speaker for Eli-Lilly, Novartis, Teva, and Allergan/Abbvie.

FundingWe declare that we have not received any scholarship, nor grant, nor help to do the MAB-MIG registry. **Authors' contributions**

- RB: Registry coordinator, Member of the Scientific Committee, Choice of variables and base design, Patient recruitment, Data management, Statistical analysis, Redaction of the paper.
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Abbreviations

CM – Chronic migraine

HFEM – High Frequency Episodic Migraine

BoNT/A - Botulinum toxin type A

WHO – World Health Organization.

CGRP - Calcitonin Gene-Related Peptide.

MRI - Magnetic Resonance Imaging.

Tables

Table 1. *Clinical Responses and Patient-Reported Outcomes (PROs) at the baseline period and after week 12 of treatment.*

Variable	Baseline	Week 12	Difference
MMD	17.1 days	11.0 days	-6.5 days
MHD	23.5 days	14.9 days	-8.6 days
HIT-6 score	68.8 points	57.2 points	-11.6 points
MIDAS score	101.9 points	66.9 points	-35 points
MOH	70%	43.4%	-26.6%

Table 2. *Predictors of response.*

Variable	Responders	No responders	p
Age	47.4 y	45.9 y	0.557
Gender (women)	46,4%	53.6%	0.294
Aura	50%	34.9%	0.088
Chronic Migraine	37.1%	62.9%	0.727
Episodic migraine	40.9%	59.1%	0.907
MOH	42.1%	61%	0.039
Prior OnabotA	37.4%	40.%	0.867
Erenumab 70mg	36.4%	63.6%	0.760
Erenumab 140 mg	39.7%	60.3%	0.648
Simultaneous OnabotA	59,6%	40.4%	<0.001
Simultaneous oral preventives	34,1%	65.9%	0.213

Table 3. *Adverse events collected during the 12-weeks of erenumab therapy.*

Adverse effect	Absolute number and percentage
Constipation	16 (7.6%)
Flu-like symptoms	8 (3.8%)
Pruritus after injection	6 (2.8%)
Fatigue	5 (2.3%)
Dizziness	3 (1,4%)
Nausea after injection	3 (1.4%)
Upper respiratory tract infection	2 (0.9%)
Skin rash after injection	2 (0.9%)
Lymphadenopathy	1 (0.4%)
Serotoninergic syndrome	1 (0.4%)
Loss of sexual desire	1 (0.4%)
Melanoma	1 (0.4%)
Diarrhoea	1 (0.4%)
Myalgia	1 (0.4%)
Injection site pain	1 (0.4%)
Muscular spam	1 (0.4%)
Panic attack	1 (0.4%)
Palpitations	1 (0.4%)
Dehydration	1 (0.4%)
Hypermenorrhoea	1 (0.4%)

Death	0 (0%)
Total	57

Figures

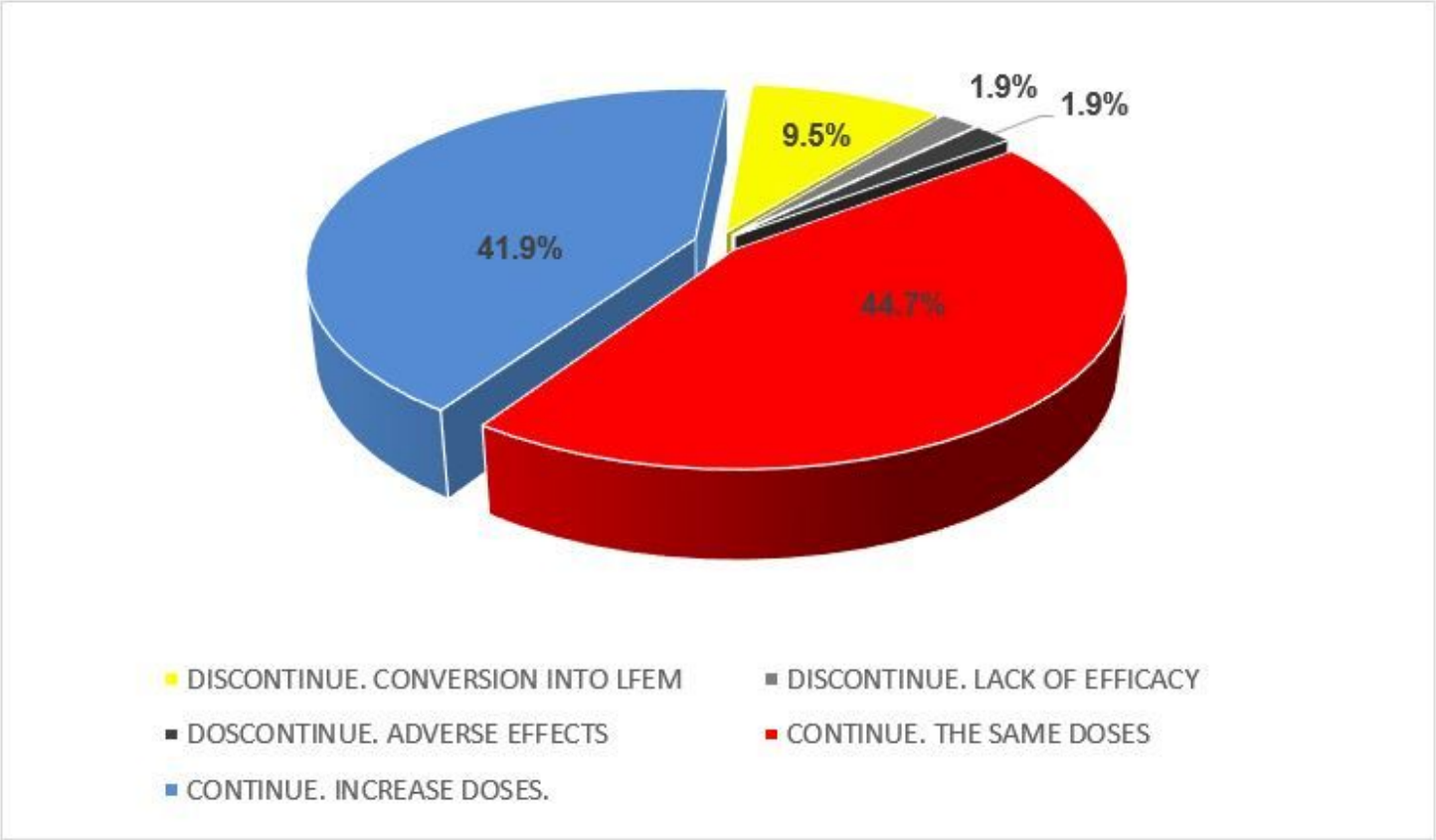

Figure 1

Sector graph showing clustering of the 210 migraine patients according to erenumab response after 12-weeks of treatment.