Non-responder migraine patients to a first anti-CGRP monoclonal antibody benefit from a switch to a second one

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Galcanezumab, erenumab and fremanezumab are monoclonal antibodies (mAb) targeting either calcitonin gene-related peptide (CGRP) or its receptor. All of them were recently approved for migraine prevention and are funded in patients refractory to a minimum of three preventive treatments with at least eight migraine days per month [1].

Clinical trials evaluated these mAb's safety and efficacy after 12 weeks of treatment. Nevertheless, interchangeability between them was not studied and, to date, there is few data published regarding it. López-Moreno et al [2] shared in this journal their experience of switching in 14 patients and we would like to contribute with our data of 60 patients (of 253 patients treated) that have switched mAbs (January 2020-June 2022) due to partial response or intolerance.

The latest *Clinical practice guidelines for headache* of the Spanish Society of Neurology's Headache Study Group [3] suggests using a different CGRP-mAb in the event that the first CGRP-mAb is ineffective.

As discussed by López-Moreno et al a significant percentage (64%) of non-responder patients showed benefit from switching to a second mAb with a different mechanism of action. Patier-Ruiz et al [4] evaluated the switch from erenumab to galcanezumab in 15 patients due to lack of response. Eight of fifteen showed a reduction ≥30% in migraine days per month compared to baseline with the second mAb (four of which achieved ≥50%), concluding that some patients may benefit from the switch. A multi-center study analyzed the switch in 78 patients due to intolerance or therapeutic failure, being one-third responders (reduction of migraine days per month ≥30%) [5]. Other case series [6,7] report an effective switch between mAb due to therapeutic failure or adverse effects in three and seven patients, considering the treatment effective if it significantly decreases headache days and/or intensity.

Clinical trials evaluated the decrease in migraine days per month or headache days per month compared to baseline, being efficacious the treatment that decreases ≥50%. Nevertheless, in clinical setting, anti-CGRP mAb have shown a reduction in pain intensity too and an improvement in work productivity, improving thereby life quality [8]. Thus, we considered the mAb effective if it decreases the number of migraine days per month/headache days per month by at least 50% compared to baseline, as well as if quality of life improves significantly –measured by Headache Impact Test-6 (HIT-6) and Migraine Disability Assessment Scale (MIDAS)–. Partial response is considered when the decrease is <50% and then a switch is proposed. As per our hospital's protocol, the second mAb was initiated one month after the last dose of the previous mAb and is maintained up to 12 months. Treatment adequacy is evaluated after three, six and 12 months. Reasons for continuation, switching and discontinuation of treatment were obtained from medical records (approved by the Ethics Committee of our center: EO_2021/17).

Patients' characteristics and persistence are described in the table. Sixty patients changed mAb. Treatments are initiated with galcanezumab or fremanezumab and are switched to erenumab 140 mg if partial response and/or adverse effects. Two patients initiated with galcanezumab and changed to fremanezumab (since the reason for discontinuation was adverse effects). Response after three months is available for 54 patients, after six months for 51 and 45 patients completed the year-treatment. Of note, patients 53-57 are patients that were previously treated with one-year of the first mAb and reinitiated it after worsening. Patients 58-60 did not stop the first mAb after 12 months due to high likelihood of worsening if discontinuation.

Overall, 70% of patients (38/54) continue treatment after three months due to effectiveness and tolerance. Persistence decreases to 42% (19/45) after 12 months of treatment. These results go along with López-Moreno et al's (rate of responders at 3rd month: 64%; persistence decreases to 25% in patients with follow-up between 6th and 12th month).

Fifty-two patients suspended the first mAb owing to partial response and/or partial response + adverse effects. Of these, 46 patients completed three months with the second mAb and 13 (28%) suspended due to partial response again. Nineteen (51%) of 37 patients with data available after 12 months suspended the second mAb due to partial response during the whole study period.

Adverse effects motivated first mAb discontinuation in 14 (23%) patients of the study population. Of the 45 patients with information after 12 months, five (11%) suspended due to adverse effects or adverse effects + partial response. Regarding the 14 patients that stopped the first mAb due to intolerance, only one patient (7%) suspended the second mAb after three months because of intolerance again and another one (7%) between the 3rd and 12th month.

Taking into account the limitations of our study, switching mAbs seems an effective and safe alternative when intolerance or partial response to the first one. A significant percentage of patients (70% three months after and 42% 12 months after) are rescued with a second mAb, being the change in the therapeutic target a feasible explanation. These results go along with previously mentioned studies [4-7]. Nevertheless, our criteria for considering a mAb effective include quality of life evaluation, something only included in López-Moreno et al's effectiveness analysis (HIT-6 and MIDAS scales). Besides, the percentage of reduction in migraine days per month also differs from our study to Patier-Ruiz et al's and multi-center

Table. Patients' characteristics and persistence with second mAb after three, six and 12 months of treatment.

				First mAb			Second mAB						
	Sex	Age	Dx	mAb	DOT (months)	Reason for discontinuation	mAb	Continuation after 3 months of treatment (YES/NO/ND)	Reason for discontinuation	Continuation after 6 months of treatment (YES/NO/ND)	Reason for discontinuation	Continuation after 12 months of treatment (YES/NO/ND)	Reason for discontinuation
1	W	78	CM	G	3	AE (vertigo)	E	YES	–	YES	–	YES	–
2	W	46	CM	G	6	AE (vertigo)	E	YES	–	YES	–	YES	–
3	W	58	CM	G	4	AE (pruritus and arterial hypotension)	E	YES	–	YES	–	YES	–
4	W	36	CM	G	6	AE (vertigo)	E	NO	PR	NO	–	NO	–
5	W	45	CM	G	6	AE (constipation and vertigo)	F	NO	AE (vertigo)	NO	–	NO	–
6	W	54	EM	G	3	AE (skin rash)	F	YES	–	NO	AE (skin rash)	NO	–
7	W	62	CM	F	3	AE (skin rash)	E	YES	–	NO	PR	NO	–
8	W	33	CM	G	6	AE (vertigo)	E	NO	PR	NO	–	NO	–
9	W	45	CM	G	6	PR	E	NO	PR	NO	–	NO	–
10	W	41	CM	G	6	PR	E	YES	–	YES	–	YES	–
11	M	56	CM	G	9	PR	E	YES	–	YES	–	YES	–
12	W	66	CM	G	3	PR	E	YES	–	YES	–	YES	–
13	W	52	CM	G	9	PR	E	YES	–	YES	–	YES	–
14	W	58	CM	G	6	PR	E	YES	–	YES	–	YES	–
15	W	33	CM	G	6	PR	E	YES	–	YES	–	YES	–
16	W	53	CM	G	3	PR	E	YES	–	YES	–	YES	–
17	M	72	CM	G	9	PR	E	YES	–	YES	–	YES	–
18	W	25	CM	G	6	PR	E	YES	–	YES	–	YES	–
19	M	54	CM	G	6	PR	E	YES	–	YES	–	YES	–
20	W	27	CM	G	6	PR	E	YES	–	NO	PR and AE (skin rash)	NO	–
21	W	48	CM	G	9	PR	E	YES	–	NO	PR	NO	–
22	W	71	CM	G	6	PR	E	YES	–	NO	PR	NO	–
23	W	30	CM	G	6	PR	E	YES	–	YES	–	ND	–
24	W	63	CM	G	10	PR	E	NO	PR	NO	–	NO	–
25	W	45	CM	G	5	PR	E	YES	–	YES	–	NO	PR
26	W	46	CM	G	3	PR	E	NO	PR	NO	–	NO	–
27	M	83	CM	G	3	PR	E	NO	PR	NO	–	NO	–
28	W	62	CM	G	3	PR	E	YES	–	YES	–	NO	PR
29	W	37	CM	G	3	PR	E	NO	PR	NO	–	NO	–
30	W	27	EM	G	6	PR	E	NO	PR	NO	–	NO	–
31	W	46	CM	G	9	PR	E	YES	–	YES	–	ND	–

Table. Patients' characteristics and persistence with second mAb after three, six and 12 months of treatment *(cont.)*.

				First mAb			Second mAB						
	Sex	Age	Dx	mAb	DOT (months)	Reason for discontinuation	mAb	Continuation after 3 months of treatment (YES/NO/ND)	Reason for discontinuation	Continuation after 6 months of treatment (YES/NO/ND)	Reason for discontinuation	Continuation after 12 months of treatment (YES/NO/ND)	Reason for discontinuation
32	W	57	CM	F	6	PR	E	YES	–	YES	–	ND	–
33	W	49	CM	G	3	PR	E	YES	–	YES	–	ND	–
34	W	31	CM	F	6	PR	E	YES	–	YES	–	ND	–
35	M	63	CM	G	8	PR	E	NO	PR and AE (constipation)	NO	–	NO	–
36	W	51	CM	F	6	PR	E	YES	–	ND	–	ND	–
37	W	52	CM	G	3	PR and AE (vertigo)	E	YES	–	YES	–	YES	–
38	M	46	EM	G	6	PR and AE (vertigo)	E	YES	–	YES	–	YES	–
39	M	62	CM	G	3	PR and AE (sleep disorders)	E	YES	–	YES	–	YES	–
40	W	50	CM	G	6	PR and AE (post–treatment seizure)	E	NO	PR	NO	–	NO	–
41	W	64	CM	G	3	PR and AE (vertigo)	E	YES	–	YES	–	YES	–
42	W	60	CM	G	3	PR and AE (vertigo)	E	NO	PR	NO	–	NO	–
43	M	63	CM	F	12	PR	E	YES	–	ND	–	ND	–
44	W	46	CM	F	12	PR	E	ND	–	ND	–	ND	–
45	W	56	CM	F	12	PR	E	NO	PR	NO	–	NO	–
46	W	52	CM	G	12	PR	E	ND	–	ND	–	ND	–
47	W	44	CM	G	12	PR	E	YES	–	NO	PR	NO	–
48	W	56	CM	G	12	PR	E	NO	PR	NO	–	NO	–
49	M	44	CM	G	12	PR	E	YES	–	NO	PR	NO	–
50	W	52	CM	G	12	PR	E	NO	AE (vertigo)	NO	–	NO	–
51	W	53	CM	G	12	PR	E	YES	–	YES	–	YES	–
52	M	54	CM	F	12	PR	E	YES	–	ND	–	ND	–
53	M	38	CM	G	12+5	PR	E	YES	–	NO	Abandons treatment	NO	–
54	W	39	CM	G	12+8	PR	E	ND	–	ND	–	ND	–
55	W	59	CM	G	12+3	PR	E	NO	PR	NO	–	NO	–
56	M	59	CM	G	12+11	PR	E	ND	–	ND	–	ND	–
57	W	53	CM	G	12+3	PR	E	YES	–	YES	–	ND	–
58	W	88	CM	F	17	PR	E	ND	–	ND	–	ND	–
59	W	45	CM	G	15	PR	E	ND	–	ND	–	ND	–
60	W	78	CM	G	15	PR	E	YES	–	YES	–	YES	–

AE: adverse effects; CM: chronic migraine; DOT: duration of treatment; Dx: diagnosis; E: erenumab; EM: episodic migraine; F: fremanezumab; G: galcanezumab; M: man; mAb: monoclonal antibody; ND: no data available; PR: partial response; W: woman.

study's (≥50 % versus ≥30 %), so does studied population too (diagnosis of chronic migraine 95% in our study versus 50% in Patier-Ruiz et al's and 88% in the multi-center study). However, López-Moreno et al's consider the same percentage of reduction in migraine days per month and study a similar population (92.8% of patients present chronic migraine).

Targeting the CGRP is an effective tool for preventing migraine attacks. However, 51% of patients do not respond to its blockade and its receptor blockade, evidencing that CGRP is not the only peptide involved in migraine crisis, as suggested by López-Moreno et al.

Further studies with bigger samples and similar effectiveness criteria are required to assess the effectiveness and safety of switching anti-CGRP mAb. Besides, other pharmacological targets should be studied as blocking the CGRP does not prevent migraine attacks in all patients suffering from migraine.

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