Failure of monoclonal antibodies against CGRP or its receptor does not imply lack of efficacy of other drugs from the same class☆

El fracaso a anticuerpos monoclonales frente a CGRP o su receptor no implica la inefectividad a otros fármacos de la misma clase terapéutica

Dear Editor:

In August 2018, the European Medicines Agency[1] approved the first preventive medications for migraine, acting on the calcitonin gene-related peptide (CGRP) pathway. These drugs have been shown to reduce the number of headache and migraine days per month in randomised placebo-controlled clinical trials including patients with episodic and chronic migraine presenting failure of and/or poor tolerance to up to 2/4 previous preventive treatments.[2–8] In the light of the above, these drugs were approved in Europe and in Spain, with the associated costs being covered by the Spanish National Health System for patients with high-frequency episodic migraine presenting failure of 3 preventive medications and patients with chronic migraine presenting failure of 3 preventive medications including botulinum toxin.[9] Despite the availability of the Spanish national guidelines, the approval of these drugs has varied between autonomous communities, and even between hospital pharmacy departments, with justification for approving one drug or another being based on bioequivalence or efficiency criteria.

From a theoretical viewpoint, we may expect to find differences in terms of effectiveness and adverse reactions, although these will probably be small.[10,11] The therapeutic target is not exactly the same: erenumab targets the CGRP receptor, whereas galcanezumab, fremanezumab, and eptinezumab target circulating CGRP.[11–13] Erenumab is a human monoclonal antibody, whereas the other drugs are

Table 1 Demographic and clinical variables of our series.

Patient	1	2	3	4	5	6	7
Sex	W	W	W	W	W	W	M
Age	54	62	34	44	24	50	33
Migraine type	CM	CM	CM	CM	CM	CM	CM
Migraine progression time before first MAb	21 years	40 years	14 years	30 years	12 years	4 years	14 years
Preventive treatments before first MAb	BB, TPM, ZNS, PGB, AML, DLX, MLT, RBF, BTX, LSN, CDS, AnBlock (n = 12)	BB, TPM, ZNS, PGB, AML, DLX, MLT, RBF, BTX, LSN, CDS, MTZ, CoQ10, AnBlock (n = 14)	BB, TPM, ZNS, PGB, AML, DLX, MLT, RBF, BTX, LSN, CDS, AnBlock (n = 12)	BB, TPM, ZNS, PGB, AML, DLX, MLT, BTX, LSN (n = 9)	BB, TPM, ZNS, PGB, AML, DLX, MLT, BTX, LSN (n = 9)	FLN, BB, TPM, ZNS, BTX, AMT, DSV, AnBlock (n = 8)	TPM, AMT, BB, AnBlock (n = 3)
First MAb	Eren	Eren	Galc	Eren	Galc	Frem	Frem
HDM before first MAb	30	30	30	30	30	25	19
MDM before first MAb	12	14	10	12	14	10	8
HDM after first MAb	24	8	30	30	30	3	16
MDM after first MAb	8	4	9	13	12	2	4
Reason for switching medication	AE	AE	Effect.	Effect.	Effect.	Pharm.	Pharm.
Second MAb	Galc	Galc	Eren	Galc	Eren	Galc	Galc
HDM after second MAb	11	10	30	22	30	20	6
MDM after second MAb	7	6	4		6	6	6

AE: adverse events; AML: amitriptyline; AnBlock: anaesthetic block; BB: beta blockers; BTX: botulinum toxin; CDS: candesartan; CM: chronic migraine; CoQ10: coenzyme Q10; DLX: duloxetine; DSV: desvenlafaxine; Effect.: insufficient effectiveness; Eren: erenumab; Frem: fremanezumab; Galc: galcanezumab; HDM: headache days per month; LSN: lisinopril; M: man; MAb: monoclonal antibody; MDM: migraine days per month; MLT: melatonin; MTZ: mirtazapine; PGB: pregabalin; Pharm.: treatment approval by hospital pharmacy department; RBF: riboflavin; TPM: topiramate; W: woman; ZNS: zonisamide.

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humanised monoclonal antibodies.[12,13] Isolated cases have been reported of patients who respond to a drug after failure of another drug from the same class.[14] Given that decisions made by pharmacy committees are based on the available evidence, we deem it highly relevant to report a series of patients presenting adequate response to one drug following failure of other drugs from the same class.

Our series includes 7 patients with chronic migraine and prior treatment with 3-14 preventive drugs (mean, 9.5) and presenting different responses to 2 different monoclonal antibodies after 3 months of treatment. Table 1 summarises the drugs administered, the reason for drug switching, and treatment outcomes.

Migraine is the third most prevalent disease in the world and the leading cause of years lived with disability between the ages of 15 and 49 years, a period when personal, academic, and professional productivity is at its peak.[15] Unlike in other neurological diseases, the disability caused by frequent, disabling migraine attacks can be prevented with pharmacological treatments, which have been shown to reduce headache frequency and intensity, work and school absences and presenteeism, and the use of symptomatic treatments.[16] Despite the small size of our series, we feel that reporting these cases contributes new evidence to support the use of a second drug acting on the CGRP pathway in patients presenting poor response to another drug from the same family; we encourage other authors to conduct further research on the topic.

Conflicts of interest

The authors have no conflicts of interest to declare.

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J. Porta-Etessam[a,b,c,*], N. González-García[a], Á.L. Guerrero[d,e,f], D. García-Azorín[d,f]

[a] *Unidad de Cefaleas, Servicio de Neurología, Hospital Clínico Universitario San Carlos, Madrid, Spain*
[b] *Departamento de Medicina, Universidad Complutense de Madrid, Madrid, Spain*
[c] *Instituto de Investigación Biomédica, Hospital Clínico San Carlos, Madrid, Spain*

[d] *Unidad de Cefaleas, Servicio de Neurología, Hospital Clínico Universitario de Valladolid, Valladolid, Spain*
[e] *Departamento de Medicina, Universidad de Valladolid, Valladolid, Spain*
[f] *Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain*

* Corresponding author.
E-mail address: jporta@yahoo.com (J. Porta-Etessam).

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A case of late-onset osmotic demyelination syndrome☆

Un caso de síndrome de desmielinización osmótica de inicio tardío

Dear Editor:

Osmotic demyelination syndrome (ODS) is a rare, severe neurological complication of some metabolic disorders. Although rapid correction of severe hyponatraemia (< 120 mmol/L) is the most frequent trigger factor (occurring in nearly 50% of cases[1–3]), other concomitant factors have also been described, including alcohol abuse or withdrawal, hypokalaemia, hypomagnesaemia, and bulimia nervosa.[3–6] ODS mainly presents between days 1 and 14 after onset of hyponatraemia treatment, and its clinical manifestations vary considerably. The syndrome initially presents with encephalopathy, which subsequently improves and is followed by dysarthria, dysphagia, oculomotor alterations, and quadriparesis, and may progress to locked-in syndrome.[1,2] We present the case of a 30-year-old woman who was attended at our hospital's emergency department after collapsing due to loss of consciousness. She had history of alcohol, cannabis, and cocaine use; an eating disorder (probably bulimia); and chronic, compulsive use of diuretics to lose weight. During the initial assessment, the patient showed fluctuations in alertness, with alternating episodes of agitation and decreased level of consciousness. A thorough study, including blood analysis, electrocardiography, and head CT, revealed severe hypoosmolar hyponatraemia and hypokalaemia (Na 107 mmol/L; K 1.8 mmol/L; osmolality 215 mOsm/kg), significant prolonged QT interval (660 ms), and epidural haematoma; the patient was admitted to the intensive care unit. Intravenous administration of hypertonic saline solution increased blood sodium concentration by 17 mmol/L in less than 24 hours (Fig. 1A and B). A week after symptom onset, the patient was discharged with no neurological symptoms or any other alterations (Na 138 mmol/L and K 3.8 mmol/L at discharge).

Eleven days after discharge (21 days after the episode of loss of consciousness), the patient visited the emergency department due to right limb weakness, which had progressively worsened over the previous 48 hours. The neurological examination revealed mixed consistency dysphagia, dysarthria, and absent gag reflex bilaterally, with severe right-sided faciobrachiocrural paralysis, mild left-sided crural paresis, and bilateral pyramidal signs. Blood electrolyte levels were normal. She was admitted to the neurology department for assessment. A brain MRI scan revealed a well-delimited area occupying the central part of the pons, which was hypointense on T1-weighted sequences and hyperintense on T2-weighted and FLAIR sequences (Fig. 2A-C). This finding is highly suggestive of pontine osmotic demyelination. The patient started intensive physical therapy during hospitalisation, and continued with the treatment on an outpatient basis. At 3 months of follow-up, she was able to walk unaided, although mild ataxia persisted.

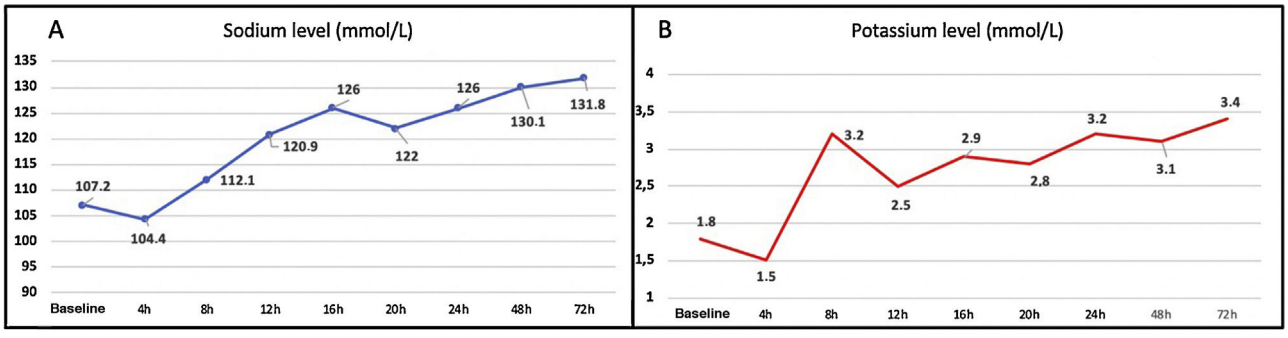

Figure 1 Sodium (A) and potassium levels (B) during the first 72 hours after admission to the intensive care unit.

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