




# SWITCHING BETWEEN ANTI-CGRP MONOCLONAL ANTIBODIES IN A CADASIL PATIENT: FOUR-YEAR EVIDENCE OF SAFETY AND EFFICACY

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**Background.** CADASIL is an autosomal dominant cerebral small-vessel arteriopathy caused by pathogenic NOTCH3 variants. Migraine, frequently with aura, is a common inaugural manifestation.Although monoclonal antibodies targeting the calcitonin gene-related peptide pathway have transformed migraine prevention, CGRP blockade in a chronically hypoperfused brain raises a theoretical hemodynamic concern, given the peptide's role as a compensatory vasodilator. Accordingly, patients with cerebrovascular disease were generally excluded from pivotal trials, and direct evidence in the use of anti CGRP monoclonal antibodies in CADASIL remains limited to isolated short-term reports, mostly involving erenumab.

**Methods.** We report a 35-year-old woman with CADASIL due to the heterozygous NOTCH3 p.Cys222Tyr variant, with arterial hypertension and depressive disorder and with childhood-onset chronic migraine with aura refractory to several preventive classes.

**Results.** Brain MRI showed confluent periventricular and subcortical bihemispheric leukoencephalopathy, with diffusely enlarged Virchow–Robin perivascular spaces and bilateral anterior temporopolar involvement. Because of near-daily attacks and marked disability, erenumab had been prescribed elsewhere, reducing attacks from daily to 7-15 days/month. At first evaluation in our center, given a stable clinical picture, a switch from erenumab to onabotulinumtoxinA was attempted; monotherapy with onabotulinumtoxinA was, however, followed by a relapse (MIDAS 103) that resolved only after reintroduction of erenumab (140 mg every 4 weeks) combined with botulinum toxin treatment according to PREEMPT protocol (MIDAS 10). In early 2025, owing to further loss of efficacy and a concomitant rise in diastolic blood pressure, treatment was switched to the anti-CGRP ligand antibody galcanezumab (120 mg every 4 weeks), achieving stable headache control (4–5 days/month) and satisfactory blood-pressure control. Serial brain MRI (every 6–12 months) confirmed morphological stability of the leukoencephalopathy throughout the four-year period (2022–2026), without new ischemic or microhemorrhagic lesions or cerebrovascular events.

**Conclusions.** Through four-year clinical-radiological monitoring, this work documents the safety and efficacy of a switch from an anti-CGRP receptor antibody to an anti-CGRP ligand antibody, combined with botulinum toxin A, in genetically confirmed CADASIL with resistant chronic migraine. Despite its single-case design, prolonged CGRP-pathway modulation proved effective and was not associated with structural cerebrovascular progression, supporting individualized strategies and prospective validation.