

Cinacalcet for Symptomatic Hypercalcemia Caused by *AP2S1* Mutations

TO THE EDITOR: Familial hypocalciuric hypercalcemia is a genetically heterogeneous disorder with three variants: types 1, 2, and 3. Type 1 is caused by calcium-sensing receptor (*CASR*) mutations,¹ and type 2 is caused by guanine nucleotide-binding protein (G-protein) subunit α_{11} (*GNA11*) mutations.² Type 3, which is the most severe variant clinically, is caused by adaptor-related protein complex 2 (AP2), sigma 1 subunit (*AP2S1*) heterozygous mutations. *AP2S1* mutations cause Arg15Cys, Arg15His, and Arg15Leu substitutions, and the mutant AP2-sigma proteins result in impaired calcium-sensing receptor-mediated signal transduction.^{3,4}

There is currently no effective therapy for familial hypocalciuric hypercalcemia type 3. We therefore evaluated the usefulness of cinacalcet, a licensed calcium-sensing receptor allosteric activator,⁵ in correcting signaling defects due to *AP2S1* mutations and in ameliorating symptomatic hypercalcemia.

We evaluated three previously unreported cases of familial hypocalciuric hypercalcemia type 3. Each of the three probands had an *AP2S1* mutation causing an Arg15Cys, Arg15His, or Arg15Leu substitution (Fig. 1A). The probands included a 34-year-old woman who had a 12-year history of hypercalcemia. She presented with fatigue, headaches, and persistent generalized aches that did not resolve after parathyroidectomy. In addition, a 22-year-old man presented with hypercalcemia, fatigue, and generalized rib pain, and a 52-year-old woman who had an approximately 20-year history of hypercalcemia presented with headaches, abdominal pain, vomiting, fatigue, and musculoskeletal pain that did not resolve after pamidronate infusion or parathyroidectomy (Fig. 1A and 1B).

The *in vitro* effects of cinacalcet on the signaling responses of cells expressing the calcium-sensing receptor and familial hypocalciuric hypercalcemia type 3-associated AP2-sigma mutants were assessed by measurement of intracellular calcium concentrations and of the activity of the mitogen-activated protein kinase (MAPK)-serum response element reporter in response to alterations in extracellular calcium (see the Methods

section in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Cinacalcet (at a concentration of 10 nM) corrected the abnormal intracellular calcium signaling and MAPK responses to extracellular calcium in cells expressing the Cys15, His15, or Leu15 AP2-sigma mutants (Fig. S1 and S2 in the Supplementary Appendix).

Oral cinacalcet (at a dose of 30 to 60 mg daily) was administered to the three probands with familial hypocalciuric hypercalcemia type 3 over a 33-to-45-month period. This treatment led to more than 20% reductions in serum calcium concentrations (Fig. 1B) and abatement of symptoms. Cinacalcet also increased serum phosphate concentrations and reduced serum parathyroid hormone concentrations, although these values remained within the normal range (Fig. 1B).

Adverse effects such as nausea, vomiting, and hypocalcemia did not develop in any of the probands. However, long-term surveillance will be required to assess safety and monitor for hypocalcemia.

Our results show that cinacalcet-mediated allosteric modulation of the calcium-sensing receptor can correct the loss of function of *AP2S1* mutations. In addition, in the short term, cinacalcet can reduce the symptoms of familial hypocalciuric hypercalcemia type 3 associated with all three *AP2S1* mutations.

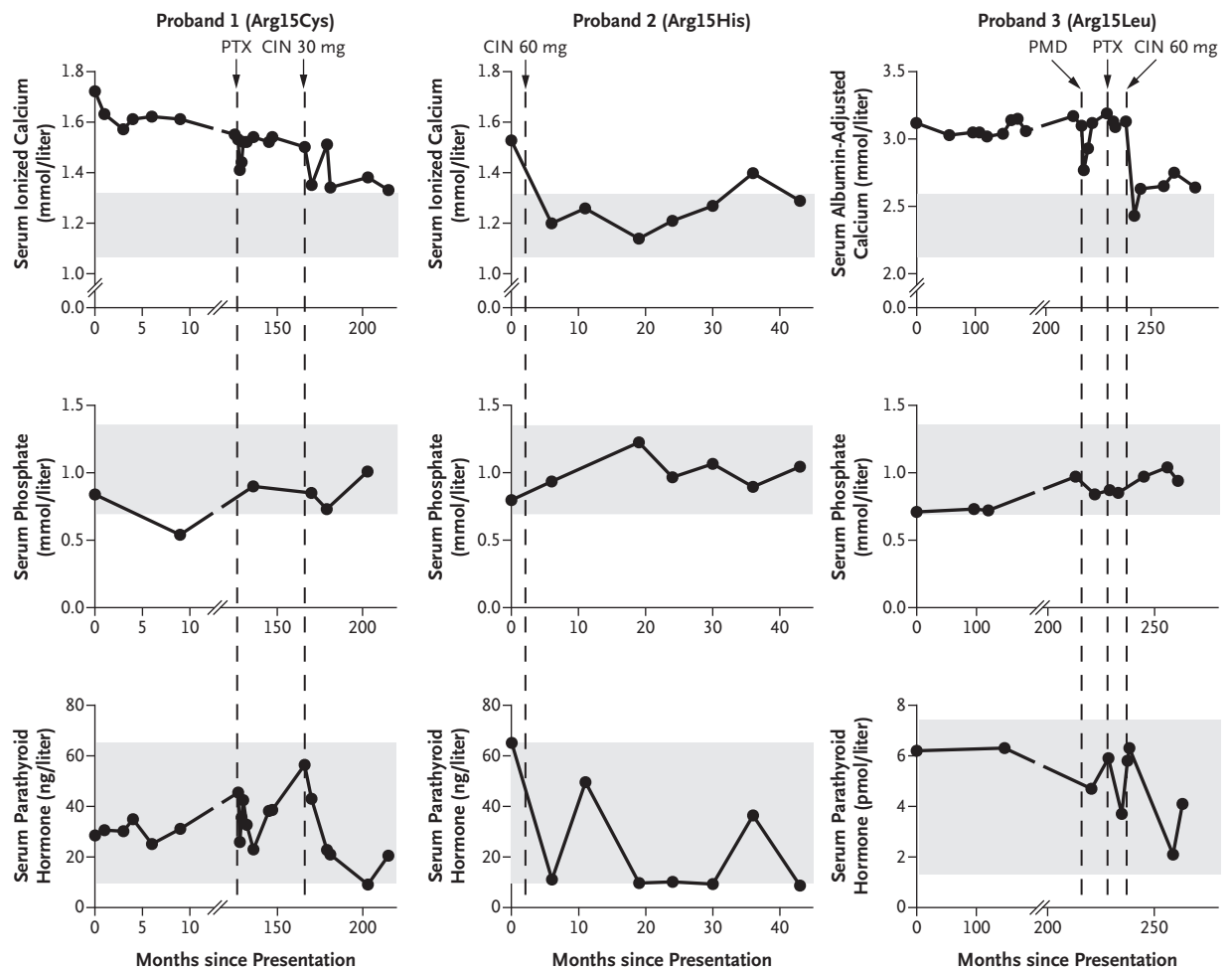
Figure 1 (facing page). Cinacalcet for Hypercalcemia Associated with *AP2S1* Mutations.

Panel A shows the clinical and biochemical findings at presentation in three unrelated probands with familial hypocalciuric hypercalcemia who had heterozygous adaptor-related protein complex 2 (AP2), sigma 1 subunit (*AP2S1*) mutations resulting in Arg15Cys, Arg15His, or Arg15Leu substitutions in the AP2-sigma mutant proteins. Reference ranges are from Nesbit et al.² Panel B shows the effect of cinacalcet on serum concentrations of calcium, phosphate, and parathyroid hormone in the three probands. Vertical dashed lines indicate initiation of cinacalcet (CIN) therapy, pamidronate (PMD) infusion, or parathyroidectomy (PTX). Shaded gray areas indicate reference ranges.

A

Variable	Reference Range	Proband 1	Proband 2	Proband 3
Sex		Female	Male	Female
Age at presentation — yr		22	22	32
Family history of hypercalcemia		Yes	Yes	No
Associated clinical features		Fatigue, headaches, generalized musculo-skeletal pain	Fatigue, rib pain	Fatigue, headaches, vomiting, abdominal and musculo-skeletal pain
Serum measurements				
Calcium — mmol/liter				
Ionized	1.10–1.30	1.72	1.53	—
Albumin-adjusted	2.10–2.60	—	—	3.07
Phosphate — mmol/liter				
Total	0.70–1.40	1.00	0.80	0.95
Alkaline phosphatase				
Total — U/liter	30–130	55.0	—	81.0
Bone-specific — μ g/liter	3.7–20.9	—	20.6	—
Magnesium — mmol/liter				
Total	0.70–1.40	0.97	—	0.98
Parathyroid hormone				
Base units	10–65 ng/liter	28.5	65.1	—
SI units	1.3–7.6 pmol/liter	—	—	6.2
Urinary calcium-to-creatinine clearance ratio				
Ratio	>0.02	0.001	0.002	0.001
AP2S1 mutation				
Mutation		Arg15Cys	Arg15His	Arg15Leu

B



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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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