Genetics in Medicine

INVITED CORRESPONDENCE

Response to Stern et al.

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We read with great interest the correspondence by Stern and colleagues describing an individual with ENPP1 deficiency who exhibited worsening vascular and valvular calcifications after initiation of burosumab, an anti-FGF23 antibody.[1] In our article, we raised a theoretical concern that FGF23 inhibition might indeed lead to worsening calcification by upregulation of alkaline phosphatase, with a consequent decrease in pyrophosphate concentrations.[2] Now Stern et al. appear to prove that this represents not just a theoretical concern, but a real risk.

Stern et al. mention that their patient had normal levels of alkaline phosphatase, calling into question whether upregulation of alkaline phosphatase could account for the worsening of ectopic calcification. A normal serum concentration of alkaline phosphatase only indicates absence of systemic upregulation, but several molecules and proteins related to the pathomechanism of ENPP1 deficiency also exert their actions at a local level. ENPP1 itself represents the main source of pyrophosphate not just systemically,[3] but also acts locally to affect pyrophosphate levels in the microenvironment surrounding vascular smooth muscle cells.[4] ABCC6 is a closely related protein participating in ectonucleotide metabolism; a deficiency of both local and systemic ABCC6 is needed to account for penetrant ectopic calcification, not a defect of either in isolation.[5] FGF23 has been shown to increase pyrophosphate concentrations through autocrine/paracrine (local) suppression of alkaline phosphatase, not via an endocrine (systemic) effect.[6] In fact, blocking increased FGF23-FGFR signaling either with anti-FGF23 antibodies or FGF receptor inhibitors has been shown to reduce local pyrophosphate levels, at least in bone.[6] In addition, local upregulation of alkaline phosphatase in vessels has been shown to lead to vascular calcification;[7,8] conversely, transgenic mice with a > 10-fold increase in serum alkaline phosphatase had no histological evidence of ectopic mineralization.[9] This highlights the different roles that circulating and membrane-bound alkaline phosphatase play in mineralization.

Regardless of the mechanism, we agree with Stern and colleagues that burosumab should be avoided in patients with ENPP1 deficiency, as it appears to lead to worsening ectopic calcification. This leads to the corollary that every patient with hypophosphatemic rickets in whom burosumab use is considered should undergo molecular testing to rule out ENPP1 deficiency.

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COMPETING INTERESTS

C.R.F. reports a collaboration with Inozyme Pharma as part of a Cooperative Research and Development Agreement (CRADA). Inozyme is developing ENPP1 as therapy for ARHR2 and GACI. S.G.Z. declares no competing interests.

ADDITIONAL INFORMATION

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