Otozomal Resesif (OR) Tip 2 Hipofosfatemik Rikets

(*ENPP1* Patolojik Varyantlarına bağlı)

Olgularında Burosomab Kullanımı Hakkında

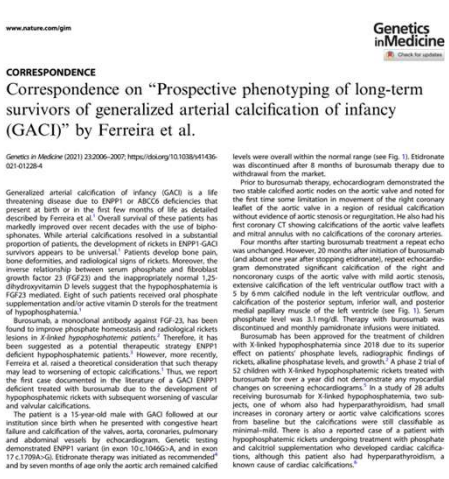
Bilgilendirme

Değerli üyeler,

FGF23 ilişkili Hipofosfatemik Rikets tedavisinde kullanılan Burosomab'ın (Crysvita) hastalığın *ENPP1* patojenik varyantlarına bağlı tipinde (OR Tip 2) kullanımı; hastalığın bir diğer özelliği olan arteriyel kalsifikasyonu arttırma riski nedeniyle uygun değildir (teorik olarak mevcut literatür bilgilerine göre) . Hastalığın tedavisi için farklı bir ilacın Faz 3 çalışması devam etmektedir [1,2,3,4] .

ÇOCUK ENDOKRİNOLOJİSİ ve DİYABET 1994 DERNEĞİ

Kemik Sağlığı Çalışma Grubu



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Genetics inMedicine

CORRESPONDENCE

Correspondence on "Prospective phenotyping of long-term survivors of generalized arterial calcification of infancy (GACI)" by Ferreira et al.

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Generalized arterial calcification of infancy (GACI) is a life threatening disease due to ENPP1 or ABCC6 deficiencies that present at birth or in the first few months of life as detailed described by Ferreira et al.[1] Overall survival of these patients has markedly improved over recent decades with the use of bisphosphonates. While arterial calcifications resolved in a substantial proportion of patients, the development of rickets in ENPP1-GACI survivors appears to be universal.[1] Patients develop bone pain, bone deformities, and radiological signs of rickets. Moreover, the inverse relationship between serum phosphate and fibroblast growth factor 23 (FGF23) and the inappropriately normal 1,25-dihydroxyvitamin D levels suggest that the hypophosphatemia is FGF23 mediated. Eight of such patients received oral phosphate supplementation and/or active vitamin D sterols for the treatment of hypophosphatemia.[1]

Burosumab, a monoclonal antibody against FGF-23, has been found to improve phosphate homeostasis and radiological rickets lesions in *X-linked hypophosphatemic patients*.[2] Therefore, it has been suggested as a potential therapeutic strategy ENPP1 deficient hypophosphatemic patients.[1] However, more recently, Ferreira et al. raised a theoretical consideration that such therapy may lead to worsening of ectopic calcifications.[1] Thus, we report the first case documented in the literature of a GACI ENPP1 deficient treated with burosumab due to the development of hypophosphatemic rickets with subsequent worsening of vascular and valvular calcifications.

The patient is a 15-year-old male with GACI followed at our institution since birth when he presented with congestive heart failure and calcification of the valves, aorta, coronaries, pulmonary and abdominal vessels by echocardiogram. Genetic testing demonstrated ENPP1 variant (in exon 10:c.1046G>A; and in exon 17:c.1709A>G). Etidronate therapy was initiated as recommended[3] and by seven months of age only the aortic arch remained calcified levels were overall within the normal range (see Fig. 1). Etidronate was discontinued after 8 months of burosumab therapy due to withdrawal from the market.

Prior to burosumab therapy, echocardiogram demonstrated the two stable calcified aortic nodes on the aortic valve and noted for the first time some limitation in movement of the right coronary leaflet of the aortic valve in a region of residual calcification without evidence of aortic stenosis or regurgitation. He also had his first coronary CT showing calcifications of the aortic valve leaflets and mitral annulus with no calcifications of the coronary arteries.

Four months after starting burosumab treatment a repeat echo was unchanged. However, 20 months after initiation of burosumab (and about one year after stopping etidronate), repeat echocardiogram demonstrated significant calcification of the right and noncoronary cusps of the aortic valve with mild aortic stenosis, extensive calcification of the left ventricular outflow tract with a 5 by 6-mm calcified nodule in the left ventricular outflow, and calcification of the posterior septum, inferior wall, and posterior medial papillary muscle of the left ventricle (see Fig. 1). Serum phosphate level was 3.1 mg/dl. Therapy with burosumab was discontinued and monthly pamidronate infusions were initiated.

Burosumab has been approved for the treatment of children with X-linked hypophosphatemia since 2018 due to its superior effect on patients' phosphate levels, radiographic findings of rickets, alkaline phosphatase levels, and growth.[4] A phase 2 trial of 52 children with X-linked hypophosphatemic rickets treated with burosumab for over a year did not demonstrate any myocardial changes on screening echocardiograms.[5] In a study of 28 adults receiving burosumab for X-linked hypophosphatemia, two subjects, one of whom also had hyperparathyroidism, had small increases in coronary artery or aortic valve calcifications scores from baseline but the calcifications were still classifiable as minimal–mild. There is also a reported case of a patient with hypophosphatemic rickets undergoing treatment with phosphate and calcitriol supplementation who developed cardiac calcifications, although this patient also had hyperparathyroidism, a known cause of cardiac calcifications.[6]

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INVITED CORRESPONDENCE

Response to Stern et al.

Shira G. Ziegler[1] and Carlos R. Ferreira[2]✉

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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

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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.

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