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EDITORIAL COMMENT

The Antioxidant Vitamin B12 Analogue Cobinamide as a Treatment for Marfan Syndrome*

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Marfan syndrome (MFS) is a relatively common autosomal dominant genetic disorder of connective tissue, with 2 to 3 per 10,000 incidences.[1] Prominent manifestations in the skeletal, ocular, and cardiovascular systems are caused by more than 1,000 mutations in the gene for fibrillin-1 (*FBN1*) and occur with great phenotypic variability. Cardiovascular manifestations with thoracic aortic aneurysms or dissections are the most severe life-threatening complications of the syndrome.[1] No correlation between the type of mutation in the *FBN1* gene and the severity of the various manifestations of the disease could be made.

Acute aortic dissection is the leading cause of death in patients suffering from MFS and is a consequence of medial degeneration and aneurysm formation.[1] In addition to its structural function in forming extracellular elastic fibers, *FBN1* regulates the bioavailability of transforming growth factor (TGF)-β stored in the matrix as part of a large complex called large latent complex in an inactive form. Dysfunctional fibrillin increases TGF-β bioavailability and concentration in the extracellular matrix, which signals via heterotetrameric complexes of type I and type II signaling TGF-β receptors activating proinflammatory transcription factors. As a result, increased expression of matrix metalloproteinases (MMPs) and cytokines control inflammatory cell migration and infiltration into the aorta.[1] Enzymatic degradation of elastin by MMPs leads to the permanent dilation of the aortic wall.

Despite the knowledge of excess mortality, hardly any elective operations were performed on patients with MFS until 1968. Only then did Hugh Bentall achieve an aortic root replacement with relatively few complications with the introduction of the composite graft, thereby decisively increasing the survival rate.[1] Surgical therapy for MFS is only the symptomatic treatment of this systemic disease; however, it remains the gold standard of treatment today. Therefore, the goal must be to treat the diagnosed patients with medication so that the development of the life-limiting aneurysm of the aortic root or ascending aorta is primarily prevented. Currently, preventive therapy consists of treatment with β-adrenoreceptor blockers, which enable more prolonged survival by reducing blood pressure in the vascular system.[1]

Recently, oxidative stress became the focus of MFS research. Reactive oxygen species (ROS) significantly participate in the pathogenesis of aortic aneurysm in MFS by the persistent high ROS production levels mediated by the xanthine oxidoreductase (XOR), the nicotinamide adenine dinucleotide phosphate oxidase (NOX)-4, endothelial cell nitric oxide synthase-3 dysfunction mediated by increased TGF-β signalling.[2] Damage to elastin and other extracellular matrix components due to oxidative stress or enzymatic degradation by MMPs is associated with alterations in the structure and function of these molecules and the progression of various cardiovascular diseases.

In this issue of *JACC: Basic to Translational Science*, Kalyanaraman et al[3] found that the vitamin B12 analogue cobinamide reduced evidence of oxidative stress and pathological changes in the aorta in male mice of the *Fbn1* $^{C1041G/+}$ mouse MFS model. Mice

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homozygous for the Cys1041Gly missense mutation (previously identified as Cys1039Gly) are small and die before 2 weeks of age. A similar Cys1039Tyr mutation is known to cause classic manifestations of Marfan syndrome in humans. Heterozygous mice show histological features of aortic disease but have an average life span and do not show severe clinical illness.

This interesting study approach using cobinamide is a follow-up to a series of published manuscripts from the Gerry Boss Laboratory, University of California-San Diego, California, USA, dealing with vitamin B12 analogue. Cobinamide is a potent, multifaceted, synthetically synthesized antioxidant, neutralizing superoxide, hydrogen peroxide, and peroxynitrite, that can treat diseases with heightened oxidative stress. They previously showed that the free radical-neutralizing vitamin B12 analog cobinamide completely prevents age-related aortic wall degeneration in $Prkg1^{R177Q/+}$ mice, having a 3-fold increase in basal protein kinase G activity.[4]

The present study is of potential interest to the field of aortic pathology. Kalyanaraman et al[3] report that cobinamide reduced aortic root dilatation, elastic fiber breaks, collagen deposition, and vascular smooth muscle cell apoptosis. Moreover, cobinamide prevented DNA, lipid, and protein oxidation and excess nitric oxide/protein kinase G signaling in the ascending aorta. It also reduced the expression of TGF-β1, NOX2, and NOX4. Finally, Kalyanaraman et al[3] used rats to determine the pharmacokinetics of cobinamide after a single-dose administration to assess that cobinamide would be a promising drug candidate.

A weak point of the study is that a survival experiment cannot be performed due to the long lifespan of the *Fbn1* $^{C1041G/+}$ MFS mouse model. The Fbn1 hypomorphic mice (mgR/mgR) are accepted as a model of MFS and are conducive to studying the clinical stages precursive to animal lethality. However, it is expected that cobinamide will also show a therapeutic effect here, as resveratrol, possessing a very high antioxidant potential, has worked well in mgR/mgR mice.[5] In addition, it will be interesting to know if cobinamide's near-complete resolution of the aortopathy of the mice is reversible once the drug is withdrawn and if the treatment causes some permanent or secondary side effects in the long run.

Altogether, this exciting paper confirms, together with others, the impact of redox stress on aortic pathology. Rodríguez-Rovira et al[2] also used heterozygous C1041G mice to investigate the contribution of XOR, which converts purines to uric acid and ROS, in MFS aortopathy. Administration of the XOR inhibitor allopurinol also significantly halted the progression of aortic root aneurysm in this MFS mouse model. Allopurinol is an active ingredient for treating elevated uric acid levels in the blood called hyperuricemia. It is used for chronic gout and has been on the market in the European Unition since the 1960s. So far, there are no human clinical studies using cobinamide. However, cobinamide may be an effective treatment option for aortic aneurysms where oxidative stress contributes to the disease, including MFS.

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