

studies^{1,2} by the addition of GH to GnRH α . Oxandrolone, a non-aromatizable androgen with a high anabolic to androgenic ratio when compared to testosterone, has been used to stimulate growth in boys with constitutional growth delay and delayed puberty. The OX administration is oral, relatively inexpensive, and devoid of significant side effects. In contrast, GH treatment requires daily subcutaneous injections, is extremely expensive, and its use may be associated with rare, although substantial side effects. This study seems to demonstrate the effectiveness of oral OX for the treatment of patients with

CPP whose growth velocities during GnRH α treatment decline significantly; however, studies in a larger number of patients, including boys, will be necessary before this modality of therapy becomes established.

Roberto Lanes, MD

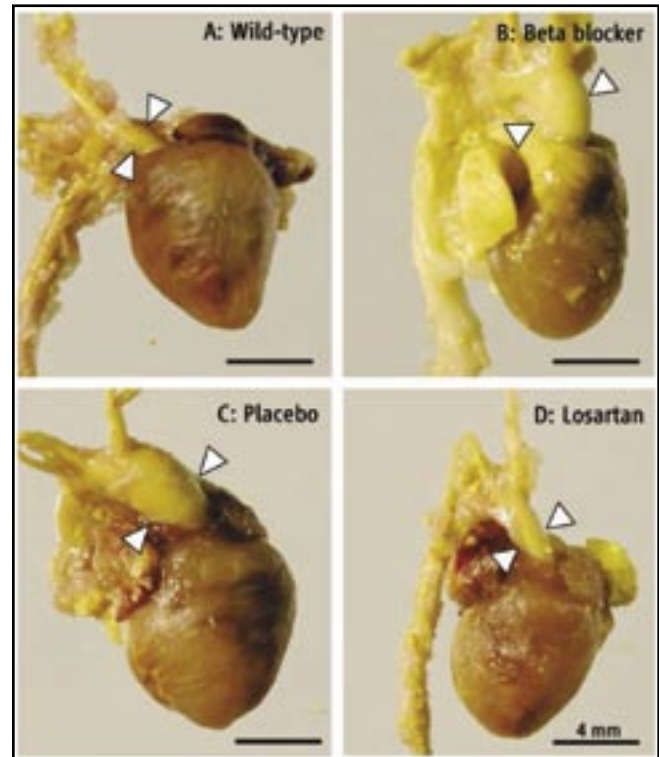
References

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Treatment for Marfan Syndrome

The Marfan syndrome (MFS) was one of the first genetic conditions designated as an inherited disorder of connective tissue. Characterized by abnormalities mainly of the skeleton, eyes and heart, the most serious manifestations involve the aorta, namely, aortic dilatation and aneurysm. Heterozygous mutations of the gene encoding fibrillin-1 (*FBN1*) were identified more than 15 years ago. *FBN1* is a principal component of extracellular matrix microfibrils; thus, it was assumed that its function was primarily structural. However, it has recently become apparent that *FBN1* binds to and influences the local availability of the growth factor TGF- β . In fact, evidence has emerged that at least some of the manifestations of MFS reflect excessive TGF- β signaling. This is because most MFS mutations are believed to reduce *FBN1* in tissues; consequently, there would be less *FBN1* to sequester TGF- β and keep TGF- β signaling in check. Indeed, mice genetically engineered to have reduced tissue levels of *Fbn1* exhibit impaired pulmonary alveolar septation associated with increased TGF- β signaling. This developmental defect can be corrected by administration of antibodies that neutralize TGF- β signaling. Much of this work has been carried out by a group headed by Dietz at Johns Hopkins. The group has now directed their attention to the role of TGF- β signaling in causing aortic aneurysm in MFS.

The authors studied mice heterozygous for an *Fbn1* mutation involving a cysteine substitution in one of the *Fbn1* epidermal growth factor-like domains; the mutation belongs to the most common class of mutations responsible for MFS. The mutant mice develop progressive aortic root dilatation evident as early as 2 weeks of age; the aortic roots of mutant and normal (wild-type [WT]) mice can be clearly distinguished by ultrasound at 7 weeks. Histologically, the aortic root of the mutant mice exhibits aberrant thickening of the media with disarray of elastic fibers and increased collagen deposition. Cells within the aortic media of the mutant mice also exhibit nuclear staining for phosphorylated Smad2 (pSmad2), which is only minimally detected in the WT mouse aortic root. Since phosphorylation of Smad2 and nuclear translocation pSmad2 are critical steps in TGF- β signal transduction, detection of nuclear pSmad2 indicates TGF- β signaling activity in these cells.



Heart of the matter. The aorta (arrows) of a normal mouse (A) and a losartan-treated mouse with a fibrillin-1 mutation (D) are indistinguishable, but those of mutant mice treated with a beta blocker (B) or placebo (C) have aneurysms.

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The 7-week-old mutant mice were treated with placebo or low- or high-dose TGF- β neutralizing antibody. After 8 weeks of treatment, aortic root growth was no different between both antibody-treatment groups and WT controls in contrast to continued dilatation in placebo-treated mice. Histology revealed substantial normalization of vessel architecture with loss of pSmad nuclear staining in both antibody-treatment groups. These data were considered consistent with the notion that TGF- β signaling contributes to aortic root dilatation in this mouse model and that TGF- β antagonism represents a potential treatment strategy for aortic disease in MFS.

The group became interested in the drug losartan, an angiotensin II type I receptor (AT1) antagonist, not only because it lowers blood pressure—a desirable effect

in patients with aortic aneurysm—but also because it antagonizes TGF- β in some circumstances. Accordingly, they initiated a therapeutic trial to determine if losartan could prevent the formation of aortic dilatation in the mutant mice. Either losartan or placebo was administered at 2-weeks gestation and continued until 10 months of age. To distinguish the effects of lowering blood pressure from those due to TGF- β antagonism, the β -adrenergic blocker propranolol was given in doses that caused hemodynamic effects comparable to those of losartan. An important advantage of using propranolol as a control is that it is commonly employed to slow aortic growth in MFS. Upon analysis, aortic root dilatation with wall thickening and elastic fiber fragmentation was detected in the placebo- and propranolol-treated mutant mice, but not in the losartan-treated mice whose aortic root measurements were virtually indistinguishable from those of WT littermates (Figure).

A postnatal trial was also done since MFS is typically diagnosed after birth and also because losartan is contraindicated during pregnancy. The researchers compared placebo, propranolol, and losartan in postnatal mutant mice beginning at 7 weeks of age at which time the aortic root diameter was greater than for WT untreated mice. After 6 months of treatment, they observed that losartan treatment prevented elastic fiber fragmentation, which was found for placebo- or propranolol-treated mice. Aortic root growth was partially normalized by propranolol, but it was indistinguishable from WT controls for mice treated with losartan. Losartan-treated mice, but not propranolol-treated mice, showed a blunting of TGF- β signaling in the aortic media cells. In short, the aortic root of losartan-treated postnatal mutant mice was comparable to that of WT control mice.

The group then showed that the distal alveolar airspaces in the lungs of postnatal losartan-treated mutant mice had sizes close to WT controls in contrast

to placebo-treated mutant mice whose airspace measurements were increased, as was expected for the mutant mice. This finding provided further evidence that the losartan effect on the aortic root is mediated by its antagonism of TGF- β rather than some unappreciated hemodynamic effect; although the authors conceded that the mechanism by which AT1 blockade antagonizes signaling is not known.

Finally, the authors discussed the potential use of losartan for treatment of MFS. They point out that losartan is currently in widespread use for treatment of hypertension and prevention of strokes in both adults and children. In an accompanying editorial, Travis states that the NIH is finalizing plans for a multicenter clinical trial of losartan for children and young adults with MFS.¹

Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312:117–121.

Editor's Comment: *The results reported in this paper are both exciting and promising. As noted, prospects for effectively treating MFS were not good when it was viewed as a disorder of extracellular matrix structure. However, in its new light as a disease mediated at least in part by excessive signaling by a growth factor, the possibilities are much better as illustrated here. The authors showed in the mouse that TGF- β antagonism can ameliorate manifestations of MFS in 2 organ systems: cardiovascular and lung. One wonders about disturbances of other organ systems, such as skeletal overgrowth. This work is a great example of successful translational research.*

William A. Horton, MD

Reference

1. Travis J. *Science*. 2006;312:36–37.

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