EDITORIAL

Of Marfan's Syndrome, Mice, and Medications

Juan M. Bowen, M.D., and Heidi M. Connolly, M.D.

Marfan's syndrome was once a disease of unknown cause, and those affected often died young from aortic dissection. Today, most patients with Marfan's syndrome who receive comprehensive care have a near-normal life expectancy. Initial therapeutic strategies evolved from clinical research done before the disease pathogenesis was understood. They include prophylactic composite aortic repair, which reduces the threat of aortic dissection, and beta-blockade, which provides medical aortic protection.

An understanding of the disease pathogenesis from basic research has resulted in new treatment strategies.[1] Mutations in the gene encoding fibrillin-1 were shown in 1991 to be the cause of Marfan's syndrome.[2] Fibrillin-1 is both a structural protein and a regulator of the transforming growth factor β (TGF-β) signaling pathway. TGF-β dysregulation results in excessive signaling, which produces the morphologic alterations recognized as Marfan's syndrome. In a mouse model of Marfan's syndrome, suppressing TGF-β signaling by blocking the angiotensin II type 1 receptor with losartan resulted in an impressive reduction of aortic dilatation as compared with placebo and beta-blockade.[3] A small series evaluating losartan in pediatric patients with Marfan's syndrome suggested that the benefits observed in mice might extend to humans.[4]

Several trials have been published subsequently. One study enrolled 28 patients with Marfan's syndrome who had an aortic z score of more than 2.0 (aortic-root diameter, >2 standard-deviation units larger than age-matched controls). The annual rate of aortic dilatation was lower in the group treated with both losartan and the beta-blocker than in the group treated with the beta-blocker alone.[5] The Cozaar in Marfan Patients Reduces Aortic Enlargement (COMPARE) trial (Netherlands Trial Register number, NTR1423) reported data from 233 adults with Marfan's syndrome who were treated with standard therapy, with or without the addition of losartan; 75% of the patients in the losartan group were also treated with a beta-blocker. The addition of losartan was again found to decrease the rate of aortic dilatation.[6]

The study by Lacro and colleagues,[7] the results of which are now published in the *Journal*, is a large trial evaluating angiotensin-receptor blockade in patients with Marfan's syndrome. Many expected the trial by Lacro et al. to confirm the superiority of losartan over atenolol in reducing rates of aortic growth. However, the trial showed no benefit in the rate of aortic dilatation when losartan was compared with atenolol over a 3-year period. The critical question is whether this finding argues for the rejection of losartan as a therapeutic option, or whether the study design masked its true benefit. We believe the answer is, Let's wait and see.

First, the study design compared losartan with atenolol, with no placebo group. Treatment guidelines recommend beta-blockers as standard therapy on the basis of the best available evidence. Beta-blockers were first shown to control aortic enlargement in a trial involving 70 patients with Marfan's syndrome.[8] Results from other beta-blocker trials have been mixed, and questions about dose and selection of beta-blocker remain. It is possible that the atenolol dose used in this trial was more effective than the investigators had anticipated. Therefore, both beta-blockade and angiotensin-receptor blockade may be effective and equivalent treatments for aortic protection.

Second, the investigators chose losartan doses that seemed appropriate during planning, but

there is no agreed-on biomarker or clinical end point that indicates the effective suppression of TGF-β signaling. Future studies may show higher or lower doses to be superior. Also, if both beta-blockers and angiotensin-receptor blockers are effective, is it possible that in combination they might work synergistically to achieve even better results? This may be the explanation for the apparent inconsistency between the results of the trial by Lacro et al. and those of the two prior studies.[5,6]

Finally, the characteristics of the patients may explain the results. The age range (6 months to 25 years) and aortic z scores (>3.0) of the patients included in this trial suggest advanced aortic disease. In the mouse, losartan was given in an early stage of development. In later stages, the aorta may be more resistant to TGF-β suppression.

The results of the trial by Lacro et al. will stimulate healthy discussion about future directions in research and treatment. These findings indicate that clinicians should continue to consider beta-blockers to be the primary medical therapy for aortic protection in Marfan's syndrome. Losartan appears to be a reasonable treatment option, especially in patients who cannot take beta-blockers. The risk of harm from losartan appears to be very low, but its efficacy needs to be firmly established before it becomes a first-line therapy.

The promise of translational medicine in Marfan's syndrome is that knowledge gained through basic research will result in treatments that change the natural history of the disease so that its clinical manifestations are attenuated or even prevented. TGF-β suppression with angiotensin-receptor blockade has not yet proved to be this breakthrough, but we await results from additional trials and a planned meta-analysis. Each step forward gives hope to those living with Marfan's syndrome as they strive to live healthier, longer, and more productive lives.

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From the Divisions of Primary Care Internal Medicine (J.M.B.) and Cardiovascular Diseases (J.M.B., H.M.C.), Mayo Clinic, Rochester, MN.

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