



Novel pharmacological strategies to prevent aortic complications in Marfan syndrome

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Abstract

The Marfan syndrome (MFS) is a systemic connective tissue disorder caused by mutations in the FBN1 gene. Recent molecular studies, most performed in mouse models, revealed that the MFS is more a developmental abnormality with broad and complex effects on the morphogenesis and function of multiple organ systems. FBN1 haploinsufficiency and dysregulated transforming growth factor-beta (TGF- β) signaling seem to be critical for clinical manifestations in MFS including aortic root dilatation. Aortic root aneurysm and aortic dissection represent the main causes of morbidity and mortality in MFS. Most importantly, TGF- β antagonism through angiotensin II type 1 receptor blockers (ARBs), for example losartan, has been shown to prevent and possibly reverse aortic root dilatation in a mouse model of MFS. A first human study on a small pediatric cohort confirmed those promising results in reducing the aortic root growth over a follow-up period of 12 to 47 months. So, a large multicenter trial has been set up and results should be available soon. Other therapeutic strategies which might be combined with losartan include traditional β -blockade, doxycyclin and statins. Such management could offer the first potential for primary prevention of clinical manifestations in MFS.

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1 Introduction

Aortic root aneurysm, subsequent aortic dissection and rupture are the leading causes of morbidity and mortality in individuals with Marfan syndrome (MFS).^[1,2] The MFS is an inherited systemic connective tissue disease that affects up to 1 in 5000 individuals.^[3] It affects both males and females, and it involves abnormalities of a variety of organ systems including aortic root dilatation, ectopia lentis, skeletal features, emphysema, dural ectasia and myopathy.^[4] Diagnosis of MFS can be difficult but has been simplified by the recently published new Ghent criteria focusing more on aortic root enlargement and ectopia lentis.^[5] If untreated, the majority of individuals with MFS develop life-threatening acute aortic events early in adult life. Prophylactic aortic surgery has been the only real therapeutic option for patients with MFS and an enlarged aortic root. Advances in surgical technique, in particular the Bentall procedure (implantation of a valved conduit) and the aortic valve-sparing root

procedure (reimplantation of the valve into a conduit), have improved life expectancy in MFS.^[2] Elective aortic surgery is now associated with low perioperative morbidity and mortality in experienced centers, and long-term survival of such patients is comparable to an age-matched healthy population.^[2] However, aortic surgery is a major surgical procedure, and in particular children with severe MFS often undergo several such operations. An improved pharmacotherapy not only treating arterial hypertension and associated aortic shear stress but targeting the cause of MFS and as such preventing aortic complications is needed.^[4]

2 Genetics and molecular pathogenesis of MFS

Mutations in the fibrillin-1 (FBN1) gene cause MFS.^[3] Most mutations occur within repeated epidermal growth factor-like domains. Such perturbations lead to enhanced proteolytic degradation and malfunction of FBN1.^[4] FBN1, a 350-kDa glycoprotein, is a principal component of the extracellular matrix microfibril. Due to the mutation, there is a severe deficiency of FBN1 aggregates in the connective tissue that would otherwise instruct the formation and homeostasis of elastic fibers and the anchorage of smooth muscle cells (SMC).^[6] As such, the MFS was originally believed to result from the production of mutant FBN1 that leads to a structural weakness of the tissue. However, recent

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progresses in understanding the complex molecular pathogenesis of MFS have challenged this view. It has been shown that the MFS is more a developmental abnormality with broad and complex effects on the morphogenesis and function of multiple organ systems. Most studies were done in mouse models of MFS and showed that microfibrils and herein FBN1 normally bind the large latent complex of the cytokine transforming growth factor β (TGF- β).^[7,8] Most importantly, failure of this interaction results in increased TGF- β activation and signaling which lead to clinical manifestations of MFS including aortic root dilatation, emphysema, mitral valve prolapse.^[7,9,10]

3 Traditional pharmacotherapy

β -adrenergic blockade, e.g., propranolol or atenolol, is traditionally used for treatment of aortic root growth in MFS. Its rationale includes reduction in arterial pressure and heart rate leading to decreased shear stress on the aorta, in particular the aortic root.^[11] Studies addressing the efficacy of β -blockade in MFS concluded that such therapy is successful at least in a subset of individuals. Overall, medicated patients showed slower aortic root growth, fewer cardiovascular endpoints and improved survival.^[4,11,12] Therefore, it is still the standard therapy for preventing aortic root dilatation in MFS. It is important to point out that β -blockade does not stop or reverse aortic root dilatation but typically slows the aortic root growth in MFS. β -blockers also do not protect the aortic wall architecture from degeneration and elastic fiber disarray as shown in mouse models and human samples. In addition, β -blockers have no effect on other clinical manifestations of MFS, and more than 10% of patients are intolerant to such therapy because of asthma, depression, or fatigue.^[4]

4 Angiotensin II type 1 receptor antagonists as novel therapeutic strategy

The rationale for the use of angiotensin II type 1 receptor (AT1R) antagonists (ARBs), e.g., losartan, developed from studies showing that MFS and associated aortic root enlargement are caused by dysregulation of TGF- β signaling and activation.^[4,7-9,13,14] Proof for the cause and effect relationship of TGF- β dysregulation came with the demonstration that a neutralizing antibody for TGF- β rescued aortic root growth in mice heterozygous for a mutant FBN1 allele (C1039G/+).^[9] Unfortunately, the application of TGF- β neutralizing antibodies is not practical in humans with MFS. Therefore, losartan came to attention

because of its known effect in antagonizing TGF- β in chronic renal insufficiency and cardiomyopathy. A blinded randomized study comparing the efficacy of losartan with propranolol was undertaken.^[9] It showed that mice with MFS treated with β -blockade have a reduction in the aortic root growth rate compared with placebo mice; however, the growth rate was still greater than in wild-type mice. In contrast, mice with MFS treated with losartan could not be distinguished from wild-type mice by any parameter including absolute aortic root size, aortic root growth rate, wall thickness or histological architecture. Subsequently, a first human study on 18 pediatric patients, aged 1 to 16 years, with a severe form of MFS were given losartan (or irbesartan) partially combined with β -blocker and/or angiotensin converting enzyme (ACE) inhibitor therapy. After a follow-up of 12 to 47 months, a significant reduction in the rate of aortic root dilatation was shown.^[15] A multicenter randomized clinical trial comparing losartan with β -blocker therapy in children and young adults with MFS and aortic aneurysm was set up and will aim to answer many of the questions on MFS and ARB therapy.^[16] This trial recently finished enrolling more than 600 participants, and data should be available soon. At least 9 other prospective studies on ARB therapy alone or in combination with β -blockade for treating aortic root dilatation in MFS are underway. A recently presented trial in 28 individuals with MFS showed that the combination of losartan and β -blockade (atenolol or propranolol) provides more effective and safe protection to slow down and even reduce the aortic root and sino-tubular junction diameter than sole β -blockade in MFS.^[17] So, it may now be tempting to treat all patients diagnosed with MFS with losartan or another ARB, also based on its safety profile. Debates on a possibly increased risk of cancer after ARB therapy were refuted in a recent meta-analysis.^[18] However, a contraindication for ARBs exists in pregnancy. More researches on the precise mechanism of ARBs in treating aortic root dilatation and other clinical manifestations in MFS are needed. Further questions need to be addressed as for example, will the effect of ARBs be consistent and significantly better than achieved with β -blockade over the long-term? Will there be unanticipated side effects in patients with MFS? Are there any effects of ARBs on other aortic parts than the aortic root? What is the consequence of stopping ARBs, recent research indicates that an extensive TGF- β activity rebound will result? This is of particular interest in women with a planned pregnancy. And what is the effect of other ARBs than losartan, e.g., candesartan or irbesartan, in which a higher dosage can be administered?

5 Other pharmacologic strategies

ACE inhibitor therapy is used either alone or in combination with β -blockade for individuals with MFS. The rationale for its use is an involvement of the renin-angiotensin system in the development of aortic stiffening and growth. A small study on 10 subjects revealed a reduction in the aortic stiffness and aortic root diameter in patients with MFS and aortic dilatation.^[19,20] However, recent research indicates that AT1R blockade may be more effective and ACE inhibitors act more like β -blockers through arterial pressure reduction.^[6,21]

Some data also indicate that interacting with molecular mechanisms responsible for the aortic wall destruction (e.g., matrix-metallo-proteinases, MMPs) may be an effective strategy. Preliminary evidence suggests that doxycycline, a tetracycline antibiotic and nonspecific inhibitor of MMP-2 and MMP-9, can attenuate aortic root growth in a mouse model of MFS.^[22,23] Most important, both TGF- β and MMP-2/MMP-9 signaling are crucial in mediating aortic pathogenesis in MFS and potential cross talk between these molecules has been demonstrated.^[24] As such, combining losartan and doxycycline may be an attractive strategy showing first promising clinical results at preventing aortic complications.^[25]

If statins, e.g., pravastatin, which inhibit MMPs at the post-translational level could affect aortic root growth in MFS needs further investigation, but some data suggest a reduction in the aortic root dilatation, at least in a mouse model of MFS.^[26]

6 Perspectives

The MFS has evolved from a structural disease to a more functional disorder with the TGF- β pathway as a critical process in its pathogenesis. Ongoing efforts are aimed at identifying events parallel to or downstream of TGF- β signaling that could serve as pharmacological therapeutic targets. The ARB therapy might be the most promising treatment option. However, results of several ongoing clinical studies are needed to allow any recommendations.^[16] Even if some negative data will be published, more recent therapeutic targets have been defined, e.g., the TGF- β mediated extracellular signal-regulated kinase (ERK1/2) activation is a predominant driver in aortic aneurysm dilatation in MFS, and as such ERK1/2 inhibitors may be a therapeutic strategy.^[21,27] In addition, circulating TGF- β and/or analysis of the ERK1/2 activation status may permit the optimization of dosing regimens for losartan and other pharmacological treatments.^[21,27,28] The MFS may serve as a

model for other forms of thoracic aortic aneurysm. Indeed, increased TGF- β signaling and activity has been observed in the aortic wall of non-Marfan patients with ascending aortic aneurysm, e.g., in those with bicuspid aortic valve, Loeys-Dietz syndrome and others with TGF- β receptor mutations.^[4,29-31] Activation of the TGF- β signaling might be a common pathway in aneurysm formation and as such TGF- β antagonism through novel pharmacologic strategies may find broader application.

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