Cure Hunter to Treat Marfan Syndrome; Introducing New Remedies to Target Transforming Growth Factor- Beta (TGF-β)

Sayed Shahabuddin Hoseini¹, Saeed Shoar², Ahmadreza Dehpour², Mohammad Naderan¹, Nasrin Shoar³

¹Development Association of Clinical Studies, Student Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
²Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
³Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran

INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant inherited disease of connective tissues that affects 2 to 3 per 10,000 individuals. Various skeletal deformities, subluxation of eye lens, duralactasia, heart valve abnormalities, aortic aneurysm and dissection (Figure 1) are some of the complications of MFS that originate from defective connective tissue homeostasis [1-2]. In the majority of cases, the disease is caused by mutations in the FBN1 gene that encodes fibrillin-1 protein which has an important role in the maintenance of elastic fibers of the extracellular matrix [3]. Fibrillin-1 is a large protein and contains seven transforming growth factor-β (TGF-β). Under normal conditions, fibrillin-1 keeps TGF-β sequestered [4]. Certain mutations in the FBN1 gene result in defects within the region that binds TGF-β. Other mutations result in decreased synthesis or rapid degradation of fibrillin-1. Yet another set of mutations can produce abnormal fibrillin-1 proteins that can polymerize in an abnormal fashion. Irrespective of the underlying defect in the fibrillin-1 protein, the overall effect is that fibrillin-1 can no longer suppress TGF-β. Increased levels of unbound TGF-β binds and activates TGF-β receptors, initiates signaling cascades that ultimately culminate in disruption of the extracellular matrix homeostasis and clinical manifestations of MFS (Figure 1). The causative nature of these sequence of events in the development of MFS has been further demonstrated by the finding that blockade of TGF-β has been shown to be effective in the treatment this syndrome [5]. It has been shown that an increase in TGF-β levels is responsible for abnormal muscular phenotypes and decreased muscle regeneration after injury [6]. Treatment with TGF-β antagonistic agents can treat mice with Marfan syndrome [7].

In this article, we propose some TGF-β antagonistic agents that may be useful to expand therapeutic modalities for affected patients.

HYPOTHESES

The major pathology in MFS is impaired connective tissue architecture. Studies in both animal models and in human tissues have revealed an increase in TGF-β signaling because of a decline in the sequestering effects of fibrillin-1 protein [8-9]. As shown in Figure 1, TGF-β can in turn activate apoptotic pathways in smooth muscle cells of vascular wall. In addition, TGF-β can activate matrix metalloproteinase enzymes resulting in destruction of the extracellular matrix [10]. Based on the pathologic function of TGF-β, researchers have tried to block its effect using inhibitory antibodies and chemical drugs; both modalities have shown therapeutic effects [5, 11].

Given that increasing the therapeutic options for a given disease can facilitate selection of the best option for a patient and may reduce adverse effects and provide alternatives for the treatment of resistant cases, we aimed to investigate the utility of other TGF-β antagonists that have not yet been tried in MFS.

Benidipine is a calcium channel blocker that has been used in animal models of diabetes. After its administration, benidipine reduced heart ventricular TGF-β levels [12]. Ursolic acid is a triterpenoid compound founded in medicinal plants and some types of foods [13]. Murakami et al. showed that ursolic acid can compete with TGF-β in binding to its receptor and thereby can inhibit its action [14]. There are some fruits and herbs rich in ursolic acid such as apple (especially its peel), rosemary, basil, and safflower extract [13, 15-16]. Richards et al. have reported that prolactin, a hormone produced by pituitary gland and also available in a recombinant form, can inhibit TGF-β [17]. Antisense technology and monoclonal antibodies can also be used to target TGF-β if their safety and efficacy is approved [18-19]. Collectively,
these agents can lower the levels of TGF-β or inhibit its binding to receptor and attenuate its pathogenic effects in MFS.

CONCLUSION

MFS is a common hereditary connective tissue disorder. There is a growing interest in utilizing TGF-β antagonists as a therapeutic modality for MFS. Blocking TGF-β has led to a decline in aortic aneurysm manifestation in animal models [8]. In this article, we proposed some of TGF-β antagonists which have not been tested in MFS. As these drugs have not been tried in MFS, their therapeutic effects are purely theoretical. Surely, the beneficial as well as the adverse effects of such recommended therapy should be assessed in animal studies; if efficacy and safety receive approval, these new agents could then enter in human clinical trials.

REFERENCES


Figure 1: Schematic view of Marfan syndrome pathophysiology. Mutation in FBN1 gene impairs fibrillin-1 production leading to an enhanced production of TGF-β and elevated levels of matrix metalloproteinase enzyme activity that culminates in matrix degradation. Besides, TGF-β can induce apoptosis in smooth muscle cells of vasculature resulting in further weakening of the vascular walls.

19. El Chaar M, Chen J, Seshan SV, Jha S, Richardson I,