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

Sayed Shahabuddin Hoseini[1], Saeed Shoar[1, 2], Ahmadreza Dehpour[2], Mohammad Naderan[1], Nasrin Shoar[3]

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

Conflict of Interest: None declared

This article has been peer reviewed.

Article Submitted on: 5th August 2012

Article Accepted on:28th September 2012

Funding Sources: None declared

Correspondence to: Dr Saeed Shoar

Address:Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Email:saeedshoar@gmail.com

Cite this Article: Hoseini SS, Shoar S, Dehpour A, Naderan M, Shoar N. Cure hunter to treat marfan syndrome; introducing new remedies to target transforming growth factor beta. J Pak Med Stud 2013; 3 (1): 28-30

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, duralectasia, 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.

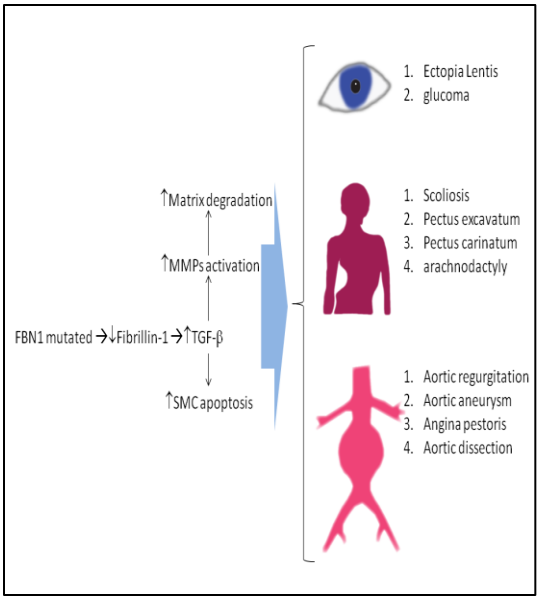
CONCLUSION

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

1. Gonzales EA. Marfan syndrome. *J Am Acad Nurse Pract.* 2009:21(12):663-70.

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 metallo-proteinase 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.



2. Judge DP, Dietz HC. Marfan's syndrome. *Lancet.* 2005;366(9501):1965-76.
3. Collod-Beroud G, Le Bourdelles S, Ades L, Ala-Kokko L, Booms P, Boxer M, et al. Update of the UMD-FBN1 mutation database and creation of an FBN1 polymorphism database. *Hum Mutat.* 2003;22(3):199-208.
4. Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, et al. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat Genet.* 200;33(3):407-11.
5. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science.* 2006;312(5770):117-21.
6. Burks TN, Cohn RD. Role of TGF-beta signaling in inherited and acquired myopathies. *Skelet Muscle.* 2011;1(1):19.
7. Cohn RD, van Erp C, Habashi JP, Soleimani AA, Klein EC, Lisi MT, et al. Angiotensin II type 1 receptor blockade attenuates TGF-beta-induced failure of muscle regeneration in multiple myopathic states. *Nat Med.* 2007;13(2):204-10.
8. Holm TM, Habashi JP, Doyle JJ, Bedja D, Chen Y, van Erp C, et al. Noncanonical TGF beta signaling contributes to aortic aneurysm progression in Marfan syndrome mice. *Science.* 2011;332(6027):358-61.
9. Nataatmadja M, West J, West M. Overexpression of transforming growth factor-beta is associated with increased hyaluronan content and impairment of repair in Marfan syndrome aortic aneurysm. *Circulation.* 2006;114(1 Suppl):I371-7.
10. Jones JA, Spinale FG, Ikonomidis JS. Transforming growth factor-beta signaling in thoracic aortic aneurysm development: a paradox in pathogenesis. *J Vasc Res.* 2009;46(2):119-37.
11. Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC, 3rd. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med.* 2008;358(26):2787-95.
12. Jesmin S, Zaedi S, Maeda S, Mowa CN, Sakuma I, Miyauchi T. Reversal of elevated cardiac expression of TGFbeta1 and endothelin-1 in OLETF diabetic rats by long-acting calcium antagonist. *Exp Biol Med* (Maywood). 2006;231(6):907-12.
13. Liu J. Pharmacology of oleanolic acid and ursolic acid. *J Ethnopharmacol.* 1995;49(2):57-68.
14. Murakami S, Takashima H, Sato-Watanabe M, Chonan S, Yamamoto K, Saitoh M, et al. Ursolic acid, an antagonist for transforming growth factor (TGF)-beta1. *FEBS Lett.* 2004;566(1-3):55-9.
15. Jager S, Trojan H, Kopp T, Laszczyk MN, Scheffler A. Pentacyclic triterpene distribution in various plants - rich sources for a new group of multi-potent plant extracts. *Molecules.* 2009;14(6):2016-31.
16. Yang YL, Chang SY, Teng HC, Liu YS, Lee TC, Chuang LY, et al. Safflower extract: a novel renal fibrosis antagonist that functions by suppressing autocrine TGF-beta. *J Cell Biochem.* 2008;104(3):908-19.
17. Richards SM, Garman RD, Keyes L, Kavanagh B, McPherson JM. Prolactin is an antagonist of TGF-beta activity and promotes proliferation of murine B cell hybridomas. *Cell Immunol.* 1998;184(2):85-91.
18. Isaka Y, Tsujie M, Ando Y, Nakamura H, Kaneda Y, Imai E, et al. Transforming growth factor-beta 1 antisense oligodeoxynucleotides block interstitial fibrosis in unilateral ureteral obstruction. *Kidney Int.* 2000;58(5):1885-92.
19. El Chaar M, Chen J, Seshan SV, Jha S, Richardson I,

Ledbetter SR, et al. Effect of combination therapy with enalapril and the TGF-beta antagonist 1D11 in unilateral ureteral obstruction. *Am J Physiol Renal Physiol*. 2007;292(4):F1291-301.