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A combination of PPAR-γ agonists and HMG CoA reductase inhibitors (statins) as a new therapy for the conservative treatment of AAS (aortic aneurysm syndromes)

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SUMMARY

The aetiology of aortic aneurysms (AAs) is the subject of intense clinical investigation. One of the critical points in their pathogenesis is the disruption of the balance between vascular extracellular matrix deposition and degradation. AAs are common features in some genetically determined diseases of the connective tissue, such as Marfan and Loeys-Dietz Syndromes. Acquired factors determining an enhanced inflammatory state of the arterial wall also play a key role. Previous studies have determined the role of TGF-β as the principal mediator of the pathogenesis of the alterations of the arterial wall homeostasis in aneurysms.

The current medical management of any AA is mainly focused on the use of pharmacological agents that reduce hemodynamic stress of aortic wall, since hypertension is the major risk factor for the enlargement and rupture of the AAs. Thus, this approach is useful to reduce the risk of aneurysm rupture but is far from being a comprehensive pathophysiology-based therapeutic approach. Drugs with the potential of reducing the action of TGF-β, which activation and expression has been reported to have a major role in the molecular pathogenesis of the aneurysms, improving matrix repair, decreasing the proteolytic pattern and inhibition of angiotensin converting enzyme as well as preventing angiotensin II-induced AT1R (angiotensin type 1 receptor) activation, can represent new options in the medical therapy of AAs. We propose that a combination of statins and PPAR-γ agonist could be a useful adjunctive therapy in this condition. The new pathophysiology-based therapeutic approach, involving the pathological patterns and mechanisms leading to the rupture of the AAs, could represent an interesting additional tool in combination with the current established anti-hypertensive therapy.

Background

Marfan syndrome (MS) is an inherited connective tissue disorder involving multiple organ systems, characterized by cardiovascular, skeletal and ocular abnormalities and results from thousands of mutations in the fibrillin-1 gene, with an estimated prevalence of 1 case per 3000–5000 individuals [1]. The most serious complications and the primary cause of morbidity and mortality in MS patients are related to the development of cardiovascular complications and, above all, aortic aneurysm dissections [2].

The aortic aneurysm is defined as a dilatation of the artery over 1, 5 times its original diameter [3,4]. It develops as a result of maladaptive remodeling of the vascular extracellular matrix (ECM), where the balance between matrix deposition and matrix degradation is disrupted, with a prevalence of enhanced proteolysis followed by an altered remodelling of the vascular ECM, with the loss of vascular smooth muscle cells [5,6]. The aetiology of an aortic aneurysm is commonly related as an idiopathic condition. However, other types of aortic aneurysm syndromes are associated with specific genetic conditions: these include MS, Loeys-Dyetz syndrome, Ehlers-Danlos syndrome and familial TAAs and dissections [7,8].

The etiological basis of AA in Marfan syndrome is ascribed to mutations in the gene encoding fibrillin-1, which is located on chromosome 15 [9]. This gene encodes for the protein fibrillin-1 (FBN1), an essential component of microfibrils that are major structural and regulatory components in the extracellular matrix. Fibrillin-1 microfibrils support cellular adhesion in the extracellular matrix via interaction with integrins and contain calcium-binding sites that are important stabilizing points against proteolytic degradation by serine proteases and matrix metalloproteinases (MMPs) [1,10]. In addition to this enhanced proteolytic degradation resulting in weakened and disordered elastic fibers, abnormalities in FBN1 function may lead to sequestration of latent TGF-β complexes in the extracellular matrix, and potentially leading to enhanced transforming growth factor-β (TGF-β) signaling [11,12]. In fact, an abnormally high level of activated TGF-β, an inducer of inflammation, fibrosis, and activation of certain metalloproteinases, such as MMP-2 and -9, has been found in Marfan syndrome [11,13]. Together, the structural microfibril matrix abnormalities, dysregulation of matrix homeostasis mediated by excess TGF-β and abnormal cell-matrix interactions are responsible for the SMC loss, elastin breakdown, accumulation of cyst-like structures

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