Ref: OT-46

Treatment and Diagnosis of Thoracic Aortic Aneurysm (TAA).

Summary:

The present invention refers to a method for the prevention or the treatment of a thoracic aortic aneurysm (TAA) in a subject, comprising administering a blocker of a new identified target of the nitric oxide (NO)-methalloproteinase pathway.

In addition, the invention further provides an in vitro method wherein specific biomarkers are used for identifying human subjects at risk of developing a disease causing thoracic aortic aneurysm (TAA). This method comprises measuring the expression pattern or level of specific NO-metalloproteinase pathway components and the expression pattern of some metalloproteinase substrates.

Lastly, the present invention refers to screening methods for identifying compounds useful for the treatment, prevention or inhibition of a TAA.

This invention apply to patients suffering from (i) bicuspid aortic valve; (ii) a syndromic thoracic aortic aneurysm (TAA) such as Marfan Syndrome (MFS), vascular Ehlers Danlos, Loeys Dietz Syndrome (Types 1 and 2), and Familial thoracic aortic aneurysm and dissection (familial TAAD); (iii) a non-syndromic TAA; or (iv) any other disease associated with an aortopathy triggered by the metalloproteinase deficiency described in the invention and based on the results obtained by the inventors which represent a substantial advance in understanding of the pathogenesis and molecular mediators underlying aortic diseases.

Innovative aspects:

Aortic aneurysm (AA) is characterized by vascular smooth muscle cell (VSMC) dysfunction and adverse extracellular matrix remodelling that together predispose the vessel wall to dilation, dissection and rupture. AA is often asymptomatic until rupture, causing significant morbidity and mortality.

TGFß activation has been proposed to cause aortic medial degeneration, but it was unclear whether it is cause or consequence of familial TAAD. Researchers' data demonstrate that blockade of the TGFß pathway did not prevent aortic dilation or medial degeneration, at least at the onset of disease, thus indicating that activation of this pathway is not causative.

In addition, previous reports implicating the NO-metalloproteinase pathway in mouse models of cerebral and abdominal aneurysm provide contradictory data, and its role in TAAD was unknown.

Researchers from CNIC have discovered that specific components levels of the NO-metalloproteinase pathway that are altered in mouse models of aneurysm aortic diseases are equally modified in MFS patients.

Thus, researchers show for the first time that said metalloproteinase is useful as a biomarker for the diagnosis of TAA through a minimally-invasive method and that inhibitors of said target of the NO-metalloproteinase pathway prevent disease development and, more importantly, have curative capacity.

Competitive advantages:

Aortic aneurysm, including both abdominal aortic aneurysm and thoracic aortic aneurysm, is the cause of death of 1% to 2% of the Western population. TAADs are responsible for significant morbidity and mortality in the young and old alike. Its incidence is ≈10,4 per 100,000 person-years. Furthermore, because acute aortic dissections might be disguised as heart attacks, ture incidence numbers could be significantly higher. The Marfan Syndrome (MFS) has a prevalence of 2 to 3 per 10,000 individuals

Despite advances in the genetics of TAAD, causative mutations have been identified for only a fraction of affected families, and no successful treatment is currently available for these diseases, including MFS. Although aortic medial degeneration and dilation are associated with activation of the TGFß and AngII pathways in syndromic and non-syndromic aortic disease, blockade of these pathways had no significant effect on treating the disease.

The AT1R antagonist losartan raised high expectations as it slows aortic growth in mouse models of MFS. However, recent clinical trials have shown that losartan in not more effective than the beta-blocker atenolol, the current standard treatment for MFS. The frustrating results with losartan evidence the need to identify new targets for intervention in aortic diseases. Our data are compatible with a role for these pathways at later stages and demonstrate that the targets identified are useful for the treatment and prevention of the disease.

Since the risk of aortic dissection or rupture escalates with increasing aortic size, the main treatment goals are to limit structural changes to the aortic wall and to slow aneurysm growth.

Our results in mouse models show that using the said inhibitors in young or in old mice reversal of dilation was remarkably fast, being complete in 1 week. Elastic fibers and collagen deposition in these mice returned to normal levels 3 weeks after treatment with the inhibitors of the above mentioned target. Long-term treatment of our mouse models showed 100% efficiency and no evidence of side effects.

Key words: Thoracic Aortic Aneurysm, TAA, Marfan Syndrome, MFS, vascular Ehlers Danlos, Loeys Dietz Syndrome, Familial thoracic aortic aneurysm and dissection, familial TAAD, non-syndromic TAAs, familial TAAD.

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