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REVIEW ARTICLE

A literature review on pharmacologic therapy for abdominal aortic aneurysms

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ABSTRACT

Aortic aneurysms affect 3.3% of adults and there is a growing burden of small aneurysms detected, which may grow to need surgical repair. Still, we rely only on surgical therapy for this disease, left to monitor patients until they are candidates for treatment. Pharmacologic therapies have long been proposed and studied and still we have no evidence supporting drug therapy in small aneurysms. In this report we make a narrative review of basic molecular aspects of aneurysm disease and of evidence behind drug therapies that have been proposed and studied throughout the last decades.

Keywords: aneurysm; aorta; pharmacology; therapy.

INTRODUCTION

Aortic aneurysms are localized dilatations of the aorta, caused by several mechanisms that weaken its wall. They may occur in any localization, be it the ascending aorta, aortic arch, descending thoracic aorta or abdominal aorta. There are, however, multiple etiologies for aortic dilation and it is known that thoracic and abdominal aneurysms are different diseases in their pathological mechanisms and progression.[1]
In this review, we focus on abdominal aortic aneurysms, the most common form of aortic aneurysm[2], in their most common form, degenerative aneurysms.

Abdominal aortic aneurysms (AAA) affect 3.3% of adults[3] and in Portugal its prevalence has been estimated at 2.1%[4] With growing awareness of the medical community and access to diagnostic exams, many of them are identified at small diameters, well before surgical indication. A significant number will grow, leading to surgical repair or rupture, with high morbidity and mortality. And still, we remain unable to halt this disease development[5], though extensive research and comprehension of molecular and cellular mechanisms, and potential therapeutic targets have been proposed.

The aim of this paper is to briefly review the evidence supporting the effect of pharmacological agents on the progression and the rupture risk of AAA.

AAA Risk Factors

Important and well-known risk factors for AAA are old age, hypertension, dyslipidemia, smoking and a family history of AAA, as well as other expressions of atherosclerotic disease, such as peripheral artery disease and coronary heart disease. [6] Diabetes, however, has been found in some cohorts to be inversely related to aneurysm disease.[7,8]

AAA Pathology

The aneurysmal aorta is characterized by loss of integrity of the extra-cellular matrix (ECM), loss of cellular function and cellular death. Damage to aortic structure has been attributed to aberrant proteolytic activity. A major factor is inflammation and oxidative stress, stimulating the expression of matrix

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metalloproteinases (MMP's) and apoptosis of smooth muscle cells (SMC's). The aortic wall is infiltrated by neutrophils, mast cells, macrophages, NK cells and T and B lymphocytes. These cells secrete chemokines, cytokines and reactive oxygen species and stimulate SMC's to secrete metalloproteinases which degrade structural proteins in the aortic wall. Several proteases have been implicated in aneurysm pathogenesis. MMP's, which degrade the ECM. Cathepsins, produced by SMC's and macrophages and neutrophil elastase, responsible for degradation of elastin, a key component of aortic wall. Granzymes, involved in cytotoxic lymphocyte-induced apoptosis, matrix degradation and disruption of the endothelial barrier function and angiogenesis. Chymase and tryptase, produced by mast cells, which activate MMP's. The TGF-ß signaling pathway is the primary pathway for production of structural proteins in the aortic ECM, and several mutations and alterations in these pathways are associated with aneurysmal disease, mostly in thoracic aorta aneurysms and connective tissue disorders but may also play a role in degenerative aortic aneurysms.

Cellular apoptosis affects mainly SMC's, which fragilizes the aortic wall not only by the loss of cellular density but also for the loss of elastin and other structural proteins production capacity.[6]

Pharmacological Therapies

Beta-Blockers

Animal studies have suggested that beta-blocker therapy, namely propranolol, may have a beneficial effect on aneurysm growth, both for its hemodynamic and biochemical effect. [9-11] On this pretense, Leach et al.[12] and Gadowski et al.[13] conducted a retrospective analysis of ß-blockers in patients with aortic aneurysms. Neither achieved statistically significative reduction in aortic expansion but in subgroup analysis, Leach et al considered the concept of rapid aneurysm expansion (>.32cm/year). In this group they found a difference of 8 to 53% (p=0.013) between treatment and control groups and Gadowski et al. found an important but still not significative decrease in expansion rate in aneurysms above 5cm. Following these works, two multicenter randomized trials were conducted. Propranolol was the drug of choice in both, and a severe limitation was common to both, which was the low compliance to treatment, caused by drug intolerance. Nonetheless, both concluded that propranolol did not inhibit aneurysm expansion.[14,15]

ACE Inhibitors

Initial evidence for ACE inhibitors came from experimental animal studies.[16,17] In 2006, a population-based case-control study[17], including 15 326 patients, proposed that ACE inhibitors were associated with a lesser probability for rupture (OR 0.82). After this study, there have been several studies contradicting these findings, particularly a prospective cohort in the UK[18], in which a faster growth rate was found in association with ACE inhibitors (3.33mm/year vs 2.77mm/year in the control group). A latter study was conducted, published in 2016, a multi-center, single-blind, randomized controlled trial named AARDVARK (Aortic Aneurysmal Regression of Dilation: Value of ACE-Inhibition on Risk)[19], which compared perindopril to placebo or placebo and amlodipine, which showed no difference in growth rate.

Statins

There are many small studies evaluating the effect of statins on aneurysm expansion, and results have been uncertain, with mixed results.[20] Recently, a systematic review[21] of these studies proposed a beneficial effect of statins, with a reduction in expansion rate, primarily in larger aneurysms and smaller rupture rates (34 vs 47%).

Antiplatelet Therapy

Antiplatelet therapy has been proposed as an expansion reduction therapy based on reduction of thrombus burden. Several small studies have been performed, with no substantial evidence. An observational cohort of 148 patients was published in 2008[22], showing beneficial effects, with a growth difference of 2.27mm, but its validity has been questioned given the extremely high growth rate in the control group (5.52mm/year). In contrast, findings in the Small Aneurysm Trial[23] and ADAM study[24] (two large population-based cohorts), contradicted this hypothesis.

NSAID's

The effect of NSAID's on aneurysm growth has been addressed, but the only study25 that reported a possible beneficial effect was highly underpowered, with only 19 patients included.

Metformin

Diabetes and aneurysmal disease have a negative association that has been well established.[26,27] However, there is evidence suggesting that this association may be in part with Metformin, a first line drug in type 2 diabetes. In 2019, a systematic review was published28 in which observational studies on the risk of aneurysm disease and also aneurysm progression, a total of 6 studies and 29 587 patients were included, finding that Metformin could effectively have a role in limiting aneurysm progression (weighted mean difference: −0.83 mm/year).

Tetracyclines

Tetracyclines, namely Doxycycline, have been proposed as potential pharmacologic treatment for their negative effect on expression of MMP's . Many animal model studies have substantiated this hypothesis[29-31] and clinical studies in humans have proved their biocellular effect.[32,33]

Three latter trials, all double-blind and placebo-controlled, have evaluated treatment with doxycycline, with varying doses and durations. Mosorin et al33 studied a cohort of 32 patients (17 in the treatment arm), given 150mg daily for three months, with higher expansion rates in the control group but showing no statistical significance. Meijner et al[34] studied a dose of 100mg daily for 18 months (286 patients; 144 in treatment arm), and found no difference between groups. Baxter et al[35] published in 2020 a study in which 133 patients were treated (in a total of 261) with 100mg daily for two years and also found no difference in aneurysm progression. Recently, a systematic review36 pooled the results of these three last studies. The composite analysis of the 572 patients (290 in the doxycycline) still didn't show significant reduction in aneurysm growth.

New molecular targets

Several studies have been developed on new molecular targets. The AORTA trial, on the effect of pemirolast, a mast cell stabilizer, a small dimension trial on canakinumab, a monoclonal antibody aimed at neutralizing IL-1ß or the effect of pioglitzone, a peroxisome proliferator-activator receptor. Though some of them showed effect on intermediate molecular endpoints, no tangible effect on aneurysm growth has been described.[20]

CONCLUSION

Many therapeutic targets have been proposed for aneurysm disease, based on our current knowledge of the basic pathophysiology of this disease. Nonetheless, there is currently no evidence of an effective pharmacologic therapy, even though some drug classes may still show some promise (statins and metformin).

Cohorts are still small and studies underpowered. Further targets are being and may still be investigated. Still, this review raises the question if our preconceptions and current understanding of aneurysm disease is as accurate as we perceive it.

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