Challenges and opportunities in limiting abdominal aortic aneurysm growth

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ABSTRACT

Objective: This review describes ongoing efforts to develop a medical therapy to limit abdominal aortic aneurysm (AAA) growth.

Methods: Data from animal model studies, human investigations, and clinical trials are described.

Results: Studies in rodent models and human samples have suggested a number of potential targets for slowing or halting AAA growth. A number of clinical trials are now examining the value of medications targeting some of the pathways identified. These trials have a number of challenges, including identifying medications safe to use in older patients with multiple comorbidities, developing accurate outcome assessments, and minimizing the dropout of patients during the trials. Three recent trials have reported no benefit of the antibiotic doxycycline, a mast cell inhibitor, an angiotensin-converting enzyme inhibitor, or a calcium channel blocker in limiting AAA growth. A number of other trials examining angiotensin receptor blockers, cyclosporine, and an antiplatelet agent are currently underway.

Conclusions: Further refinement of drug discovery pathways and testing paradigms are likely needed to develop effective nonsurgical therapies for AAA. (J Vasc Surg 2016;■:1-9.)

Abdominal aortic aneurysm (AAA) is an important cause of premature death worldwide. Recent estimates suggest an annual death rate due to aortic aneurysm of 2.8/100,000 (>20 million), representing a 12% increase in the last 20 years.[1] Although the highest death rates per year are reported in the developed regions of Australasia (8.38/100,000) and Western Europe (7.68/100,000), rapid increases in mortality rates are being reported in underdeveloped nations.[1] In the United States and parts of Western Europe, death rates resulting from ruptured AAA have fallen by >50% over the same time period, coinciding with dramatic reductions in per capita cigarette consumption, increased elective surgical repair of AAA, and improved management of cardiovascular disease risk factors.[2-7] The estimated death rate each year due to AAA in North America is 6.11/100,000.[1]

The management of AAA is guided mainly by aneurysm size and sometimes by the rate of aortic diameter enlargement during subsequent periodic surveillance imaging.[8] Small AAAs (<55 mm in diameter) are usually managed conservatively and monitored by regular imaging surveillance. Most small AAAs continue to enlarge after diagnosis and eventually undergo surgical repair.[9,10] Large AAAs (≥55 mm) are usually managed by endovascular exclusion or open surgical repair.

Currently, no medical treatments have proven effective in limiting AAA growth. This review provides an update of research being undertaken to identify nonsurgical methods of reducing the rate of AAA growth, including insights into some of the challenges experienced in this research, a discussion of outcome measures that maybe used within these studies, and current investigations to test novel treatments to limit AAA growth.

CURRENT THEORIES REGARDING AAA PATHOGENESIS

Studies investigating mechanisms of AAA pathogenesis have used animal models, aortic tissues, blood samples, and epidemiologic data.[11-21] Findings from these studies are detailed in a number of prior reviews and, therefore, are not discussed in detail here.[11-21] Advanced age, smoking, male sex, family history of AAA, and history of hypertension or atherosclerosis-associated events are all established risk factors for AAA.[22] Examination of human AAA biopsy specimens and studies in rodent models of AAA suggest that inflammation, extracellular matrix

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Table I. Potentially targetable mechanisms implicated in abdominal aortic aneurysm (*AAA*) pathogenesis

Primary mechanism	Examples of cellular or molecular processes implicated in AAA pathogenesis
Genetic predisposition	Mutations at the chromosome 9p21.3 locus and within DAB2 interacting protein (*DAB2IP*) and low-density lipoprotein receptor-related protein 1 (*LRP1*) genes
Epigenetic mechanisms	miRNAs (eg, MiR-29b)
Immune	Mast cell degranulation; neutrophils and lymphocyte- based inflammation; chemokine and cytokine production
Dyslipidemia	Low HDL; high lipoprotein(a)
Renin-angiotensin system	Angiotensin II, ACE, and renin activation
ECM degradation	Matrix metalloproteinases, granzymes, and cathepsins-mediated ECM damage
VSMC dysfunction	Enhanced apoptosis, impaired proliferation and ECM production
ECM structure and signalling	Impaired TGF-β signalling
Oxidative stress	Enhanced production of ROS
Hemodynamics	Aberrant flow within the AAA promotes thrombus formation and aberrant distribution of wall stress
Angiogenesis	Enhanced angiogenesis promotes inflammation and ECM destruction
Thrombus related	A large AAA thrombus promotes ROS production, inflammation and production of ECM degradation enzymes

ACE, Angiotensin-converting enzyme; *ECM*, extracellular matrix; *HDL*, high-density lipoprotein; *miRNA*, micro RNA; *ROS*, reactive oxygen species; *TGF*, transforming growth factor; *VSMC*, vascular smooth muscle cell.

remodelling, oxidative stress, vascular smooth muscle cell dysfunction, angiogenesis, and thrombosis are all important in AAA pathogenesis (Table I).[11-22]

Human studies with large cohorts have reported the association of a number of inherited genetic mutations with AAA, such as single nucleotide polymorphisms on chromosome 9p21.3, within intron 1 of DAB2 interacting protein (*DAB2IP*), and within intron 2 of the gene encoding low-density lipoprotein receptor-related protein 1 (*LRP1*).[17] Mice with targeted inactivation of *LRP1* within vascular smooth muscle cells are prone to aortic aneurysm formation, suggesting this gene may play a protective role against AAA.[17] The reported increased risk for AAA associated with these risk alleles is, however, only ~1.1-fold to 1.2-fold, perhaps limiting the translational potential of these observations.

Recent studies have highlighted the potential role of epigenetic regulation in the pathogenesis of AAA. MicroRNAs (miRNAs) are nonprotein-coding RNA sequences that can modulate the transcription of coding segments of DNA. The expression of a number of different miRNAs (such as miR-29b and miR-155) within the aorta or circulating blood has been associated with AAA diagnosis in small studies.[13,21] Modulating the expression of some miRNAs has been shown to promote or inhibit the development of AAA within rodent models.[13,21] For example, antagonizing miR-29b has been reported to limit aortic expansion in the angiotensin II-, elastase- and fibrillin 1-deficient mouse models by limiting aortic inflammation and extracellular matrix remodelling.[13,21]

Experimental studies have suggested the potential efficacy of a number of strategies for limiting AAA growth, including inhibiting mast cells, blocking matrix metalloproteinases, inhibiting angiogenesis, antagonizing platelet aggression, and inhibiting angiotensin II, as previously reviewed.[15,18] Translating insights derived during rodent experiments into effective treatments for small AAAs has proven challenging, however. The relevance of findings from rodent AAA studies to human AAA remains controversial.[23]

Human AAA tissue is principally available after surgical repair of advanced disease. Analysis of such samples may have limited relevance to pathogenic processes prevalent earlier in the course of the disease, when medical therapies are most likely to be effective. Inflammation, for example, is considered central to AAA pathogenesis based on findings from human biopsy specimens from end-stage AAA and rodent models; however, rapid expansion and rupture of a previously small AAA has occurred in at least one patient receiving immunosuppression after a kidney transplant.[15,18,24] Ultimately, clinical trials are required to examine the potential efficacy of any drug or strategy thought to be effective in limiting AAA growth.

DESIGNING TRIALS TO TEST NEW TREATMENTS FOR SMALL AAA

The remainder of this review focuses on the designs and findings of clinical trials that have examined the efficacy of treatments to slow AAA growth. Designing and performing such trials presents a number of challenges, including those common to most clinical trials such as obtaining adequate recruitment and retention of patients and ensuring patient compliance and consistency of data reporting. Some of the unique challenges to designing small AAA trials are summarized in Table II and considered in more detail in another review.[25] These challenges include the slow rate of AAA growth in most patients, meaning that accurate outcome assessments are very important; the frequent loss of patients to AAA repair during follow-up, which limits the ability to study AAA growth for extended periods; and the frequency of