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Review

Current status of medical management for abdominal aortic aneurysm

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ABSTRACT

Previous trials indicate that surgical management of small abdominal aortic aneurysms (AAA) does not reduce mortality. The medical management of AAA, however, has to a large degree been ignored until recently. Medical management is not only needed to limit the expansion of small AAAs but also to reduce the high incidence of other cardiovascular events in these patients. In this review current evidence regarding medical therapy for patients with small AAAs is discussed. Four current randomised controlled trials are examining the efficacy of exercise, doxycycline and angiotensin converting enzyme inhibition in limiting AAA progression. A further trial using a mast cell stabilisation agent is expected to start soon. It is anticipated that a range of novel therapies for small AAAs will be identified within the next decade.

Contents

1. Introduction

The prevalence of abdominal aortic aneurysm (AAA) is ~5% in men and ~1% in women aged >60 years [1]. Four randomised controlled trials have shown that the rupture rate of small AAAs under surveillance is only ~0.5–1%/year when intervention is undertaken if the aneurysm expands to >55 mm or becomes symptomatic [2–5]. These trials also suggest that early elective surgery in patients with 40–54 mm AAAs offers no survival advantage [2–5]. Overall mortality in these trials was 3–6%/year, with approximately 40% of deaths due to cardiovascular causes not directly related to AAA [3]. Despite the relatively low risk of aneurysm-related mortality in patients with small AAAs, a substantial proportion of subjects eventually undergo AAA repair. In the Danish screening trial 44% of AAAs measuring >30 mm eventually underwent surgery over a 14 years follow-up [6]. In randomised trials of patients with 40–55 mm AAAs where intervention was indicated for AAA progression to 55 mm or symptom development, ~70% of patients had surgical repair over 5–10 years follow-up [2–5].

Both open and endovascular repair are effective treatments for large (>55 mm) AAAs but both have limitations. Open surgery is associated with a perioperative mortality rate of up to 5% and other significant complications, as well as an extended recovery time [2,3]. Endovascular AAA repair has a lower perioperative mortality (~1%) and complication rate, as well as a more rapid recovery, however, durability is a problem and necessitates long-term imaging and clinical follow [7]. As a result the need to identify effective medical therapies which could reduce or eliminate small AAA growth and also improve overall outcome (e.g. by reducing cardiovascular events) is a major priority. In this article work centred on developing such therapy is reviewed.

2. Limitations of pre-clinical studies of medical therapy for AAAs

Examples of different strategies being used to assess the value of medical therapy for AAAs are shown in Table 1. Studies carried out *in vitro* or within animal models may suggest mechanisms relevant

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Table 1
Sources of evidence on which to base current recommendations on medical therapy of small AAAs.

Study type	Advantages	Disadvantages
Animal model Human *in vitro* study	Easy to design and control	Findings in animal models and *in vitro* may not translate into similar effects in patients
Human association study	Relatively easy to carry out	Not possible to adjust for confounding effects so conclusions difficult
Randomised trials with surrogate end-points, e.g. changes in AAA biopsies	Outcomes more rapidly obtained	May not translate into effects on clinically important end-points
Randomised trials specifically designed for patients with small AAAs	Outcomes essential in order to establish the value of strategies suggested by other study types	Require multi-centre involvement and considerable funding

Table 2
Mechanisms implicated in AAA pathology which could potentially be targeted by medical therapies.

Primary mechanism targeted[a]	Novel or existing drug targets or medications
Immune	Mast cell degranulation [9]; NF_kB [10]; c-Jun N-terminal kinase [11]; peroxisome proliferator activator α and γ [12,13]
Dyslipidemia	Statins [8,14–17]; ezetimibe [18]
Hypertension	Angiotensin II blockade [20,43–46]; angiotensin converting enzyme inhibition [43,46]; calcium channel blockers [105].
ECM degradation	Mast cell chymase [9]; matrix metalloproteinases [19–32]; granzymes [33]; cathepsins [34]
VSMC dysfunction	Caspase [35]
ECM structure and signalling	Transforming growth factor beta signalling [36]; granzymes [33]
Oxidative stress	Cyclophilin A [37,38]
Haemodynamics	Flow loading [39]
Angiogenesis	Angiogenesis inhibition [22]
Thrombus-related	Anti-platelets [40,41]

ECM = extracellular matrix; VSMC = vascular smooth muscle cell.
[a] In many cases more than one mechanism implicated in AAA is targeted.

to human AAA but translating findings into an effective therapy for patients has a number of challenges. It is difficult to simulate longer term effects of medication within human tissue *in vitro*. Given the complexity and heterogeneous nature of human AAA it is also difficult to model all features in animals. Rodents have been most commonly used in recent studies but their response to some drugs (e.g. statins) is different to humans [8].

Examples of drugs or targets which have proved effective at inhibiting AAA development or progression in animal models are shown in Table 2 and have previously been reviewed [9–46]. Defining which of these potential approaches are most suited to clinical development is complex. Important considerations include: the magnitude and consistency of effect in pre-clinical models; the estimated toxicity in humans; the feasibility of studying the particular therapy in a clinical trial; the cost of drug development; and interest from industry in contributing to drug development [47].

Given the challenges involved in developing AAA-specific medications there has been interest in assessing treatments already in use for other indications as AAA therapies. In a number of studies investigators have assessed the association of medication prescribed for associated morbidities, such as hypertension or dyslipidemia, with small AAA expansion. In addition a small number of randomised controlled trials have been carried out to assess the efficacy of some of the currently available drugs. In the following sections relevant data from animal and human studies will be discussed.

3. Clinical studies assessing the efficacy of treatments for small AAAs

Important aspects of clinical studies in patients with small AAAs include: study design (e.g. randomised prospective study vs retrospective observational study); sample size and effect size; and outcome definition. As outlined above the main goals for medical therapy in patients with small AAAs are to prevent AAA progression to rupture, reduce the long-term requirement for surgery and limit cardiovascular events. Such end-points while clinically relevant require very large studies with long-term follow-up and thus a substantial amount of funding. Given these challenges, completed, on-going and probably most planned studies use surrogate outcomes. The most common surrogate marker is the maximum infra-renal AAA diameter as it is the main determinant of when AAA repair should be planned based on risk of rupture [48]. Other surrogate outcome measures include: changes in pathological features of AAA within aortic biopsies [18,49]; concentrations of circulating biomarkers [50]; AAA volume [51]; and functional imaging findings (e.g. FDG-PET) [52]. These markers and outcomes have been recently reviewed [50].

4. Examples of therapeutic strategies of current interest

Smoking cessation: Smoking is the most important modifiable risk factor for AAAs and screening studies suggest that 18–52% of patients with small AAAs are current smokers [53–55]. In the UK small aneurysm study continued smoking predicted more rapid increase in maximum AAA diameter [56]. Although there have been no reported trials of smoking cessation in patients with AAA, it is likely that continued smoking increases the risk of cardiovascular events and as such smoking cessation remains a priority for all patients with AAAs. A number of mechanisms to assist with smoking cessation are available [57].

Exercise: A study in a rat model suggested that increased aortic flow inhibited AAA expansion [39]. Magnetic resonance imaging studies show that exercise increases abdominal aortic blood flow in patients who have AAAs and thus has potential to inhibit AAA progression [58]. A current randomised controlled trial is examining the effect of an exercise program on small AAA growth [59]. Exercise may also reduce cardiovascular events in these patients. In a preliminary report of the trial, exercise was associated with a reduction in circulating concentrations of C-reactive protein and a trend downwards in waist circumference [59]. The trial uses a combination of home-based and supervised exercise in different patients depending on feasibility. Studies in patients with intermittent claudication suggest a supervised program is more effective than home-based exercise in the short-term but recruitment and retention to such studies is generally a problem and long-term advantage less clear [60]. Whether supervised exercise programs are feasible, cost effective and would have sufficient uptake in patients with AAA is not currently known. Effective means are required to encourage exercise and other positive health behaviours in this patient group. In this regard the recent report of the use of home-based motivational interviewing sessions in patients with intermittent claudication is encouraging and relevant [61].

Beta blockers: A number of early rodent studies suggested the potential efficacy of beta blockers in inhibiting expansion of AAAs