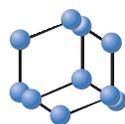


REVIEW ARTICLE


**BENTHAM
SCIENCE**

Fenofibrate and Telmisartan in the Management of Abdominal Aortic Aneurysm

*Current
Drug Targets*

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Abstract: Objective: This mini-review provides the rationale and updated progress for ongoing randomized controlled trials assessing fenofibrate and telmisartan efficacy to limit abdominal aortic aneurysm (AAA) growth.

Methods/Results: There remains an urgent need to identify a drug therapy that will limit AAA growth. Data from preclinical and human studies indicate that fenofibrate and telmisartan have the potential to slow aortic destruction. Fenofibrate has been shown to reduce serum and tissue levels of the pro-inflammatory protein osteopontin, as well as reducing macrophage recruitment to the aortic wall, both of which are integral processes in the development and progression of AAAs. Telmisartan acts *via* blockade of the angiotensin II receptor, type 1, and also as a peroxisome proliferator-activated receptor gamma agonist. In turn, this inhibits the production of a range of biomarkers associated with AAA progression, including transforming growth factor-beta one, osteoprotegerin, osteopontin and matrix metalloproteinase-9. Based on these findings, there are currently three randomized controlled trials assessing both fenofibrate and telmisartan as potential interventions to limit aneurysm growth in AAA patients.

Conclusion: Fenofibrate and telmisartan have potential as repurposed medications to limit AAA growth, and randomized trials for further assessment in AAA patients are ongoing.

ARTICLE HISTORY

Received: August 07, 2017
Revised: September 04, 2017
Accepted: December 12, 2017

DOI:
10.2174/1389450119666171227224655

Keywords: Abdominal aortic aneurysm, telmisartan, fenofibrate, osteopontin, angiotensin, clinical trial.

INTRODUCTION
1. PRESENT MANAGEMENT AND SIGNIFICANCE OF AAA

Abdominal aortic aneurysm (AAA) is a progressive destructive process of the main abdominal artery, with a prevalence of 2-5% in men and 1% in women aged over 65 years [1]. In 2010, the estimated global prevalence rate was 2,275 per 100,000 in individuals aged 75-79 years [2]. The global death rate due to AAA increased from 2.49 to 2.78 per 100,000 between 1990 and 2010, with the highest mean death rate occurring in Australasia [3]. The present management options for AAA are surgical repair (open or endovascular), or follow-up by imaging at intervals, *i.e.* conservative treatment with no therapeutic intervention [4]. In view of the increasing importance of AAA as a cause of mortality, ultrasound screening has been introduced in the United States, United Kingdom and Sweden [5]. Such screening of at risk individuals, either on a population basis or as arranged selectively by practitioners usually identifies AAAs of small size,

with 90% measuring less than 50mm [6]. Large randomized trials have failed to provide evidence that early elective surgical repair of patients with small AAAs (40-54mm) reduces mortality [7-10]. In summary, surgery does not appear to offer any solution for the increasing number of patients with small AAAs.

2. THE URGENT NEED FOR AN EFFECTIVE DRUG THERAPY FOR SMALL AAA

Due to continued aortic expansion in individuals with small AAAs, up to 70% of patients will ultimately require surgical repair [7, 10]. Thus, there is a need to identify medications that can slow aortic destruction. Such drug therapy could be used in patients with small AAAs to reduce the number later requiring surgery, in those unsuitable for AAA repair, and to reduce the need for secondary intervention in those previously treated surgically [11]. Although advisable, there is presently no evidence that control of atherosclerotic risk factors alone reduces AAA progression [12]. There have been relatively few randomized controlled trials completed to identify a drug therapy that will slow AAA growth, with no large trial demonstrating the benefit of any tested agent [13-18]. There are however a number of such trials ongoing and these have recently been reviewed in detail elsewhere [1]. To successfully be investigated in a randomized trial, a

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potential medication requires evidence to support its benefit, a good safety profile, a large proportion of individuals with AAAs in whom the medication is not already indicated, and a likelihood of good compliance. The remainder of this review will focus on two agents that fit those criteria, namely fenofibrate and telmisartan.

3. RATIONALE FOR A DRUG TRIAL OF FENO-FIBRATE IN PARTICIPANTS WITH SMALL AAAs

Pre-clinical studies have demonstrated that the peroxisome proliferator-activated receptor alpha (PPAR α) agonist, fenofibrate, reduces the development of experimental AAAs [19, 20]. Administration of fenofibrate in a mouse model inhibited AAA progression which was associated with a reduction of the pro-inflammatory protein osteopontin (OPN), and reduced recruitment of macrophages to the aortic wall [19]. OPN is a phosphorylated acidic glycoprotein which was originally identified in bone and shown to facilitate osteoclast binding to mineralized matrix [21]. Subsequently, OPN has been shown to be widely expressed in the arterial system and implicated in promoting inflammation, proteolysis and atherosclerosis, all of which are integral processes in AAA development and progression [22-27]. OPN deficiency has been shown to protect against AAA development in mice [28]. The ability of OPN to promote macrophage accumulation within the aorta appears critical in the development and progression of AAA in experimental models [28, 29].

To assess the relevance of OPN to human AAA, we examined two cohorts: a) 466 men that took part in a community ultrasound screening study in Western Australia (WA), of whom 233 had an AAA; and b) 199 patients referred for aortic imaging at a vascular centre in Queensland, of whom 132 had an AAA. The mean (\pm SD) serum OPN concentrations were 77 \pm 32 ng/ml and 66 \pm 29 ng/ml in men from WA who did and did not have AAAs, respectively, $p < 0.001$ [30]. The mean (\pm SD) serum OPN concentrations were 73 \pm 44 ng/ml and 59 \pm 44 ng/ml in patients from Queensland who did and did not have AAAs, respectively, $p = 0.001$ [30]. Serum OPN concentration was independently associated with AAA after adjusting for other risk factors in both cohorts. 198 of the men from WA underwent repeat imaging of their AAA for at least 3 years with a mean (\pm SD) increase in aortic diameter of 3.5 \pm 3.3 mm. Serum OPN was independently associated with AAA growth after adjusting for other risk factors. In patients who underwent open AAA repair, OPN expression was assessed in AAA biopsies by real time PCR and immunohistochemistry. Expression of mRNA encoding OPN and the 65 kD intact OPN protein were increased in AAA biopsies when compared to samples of normal abdominal aortas from age-matched organ donors. Furthermore, OPN staining was demonstrated within areas of calcification and macrophage infiltration in human AAA biopsies [30]. The upregulation of OPN in human AAA biopsies has been confirmed by other investigators [31, 32]. These data suggest that: a) OPN is highly associated with human AAA presence and progression; b) serum OPN may be a useful biomarker for AAA pathology; and c) OPN may promote AAA by stimulating macrophage based aortic destruction.

Macrophages appear to be a primary target of the detrimental effects of OPN [21, 22, 33, 34]. Macrophages are

implicated in aortic destruction as a result of the production of a range of proteolytic enzymes such as matrix metalloproteinases (MMPs) [11]. Previous *in vitro* studies demonstrate that PPAR α ligands downregulate OPN expression in human macrophages by rapidly inhibiting transcription of the OPN gene [35]. Fibrates are well known PPAR α agonists in clinical use for the treatment of hypertriglyceridemia [36]. Previous rodent studies demonstrate that fenofibrate downregulates OPN in left ventricle hypertrophy and dysfunctional renal cells [37, 38]. Furthermore, following four weeks of bezafibrate treatment in diabetic patients, a 23% reduction in circulating concentrations of OPN was observed [35]. Together, these data support the action of fibrates to negatively regulate OPN *in vitro* and *in vivo*.

In view of the ability of fibrates to downregulate OPN, and the significant evidence implicating OPN in AAA pathogenesis, we hypothesized that fenofibrate would inhibit aortic expression of OPN thus limiting AAA progression. As an initial test of this hypothesis, we examined the effect of fenofibrate in two established experimental models of AAA [19, 20]. First, the effect of fenofibrate (100mg/kg/d) *versus* control was examined in apolipoprotein E deficient (ApoE $^{-/-}$) mice receiving angiotensin II (AngII) infusion to induce AAA formation [19]. Fenofibrate markedly reduced aortic concentrations of OPN and associated macrophage infiltration. The median and interquartile range for aortic OPN concentration in mice administered fenofibrate or control was 126 (35-729) and 3198 (382-11138) pg/mg of protein, respectively; $p = 0.006$ [19]. The median and interquartile range for CD68 (macrophage) staining within aortas of fenofibrate and control mice was 4.0 (2.2-6.1) % and 13.2 (8.4-20.0) %, respectively; $p < 0.001$ [19]. Fenofibrate inhibited AAA progression with the maximum aortic diameter reduced from a mean (\pm SD) of 2.10 \pm 0.14 mm in control mice to 1.51 \pm 0.13 mm in mice receiving fenofibrate; $p = 0.001$ [19]. To assess the reproducibility of this finding, we examined the effect of fenofibrate in a second mouse model deficient in low density lipoprotein (LDL) receptor (Ldlr $^{-/-}$), in which AAA was induced with AngII infusion [20]. Mean (\pm SD) aortic diameters were 1.06 \pm 0.06 mm and 1.25 \pm 0.05 mm in mice receiving fenofibrate (100mg/kg/d) and control for 4 weeks, respectively; $p = 0.002$ [20]. These data demonstrate the efficacy of fenofibrate in downregulating aortic expression of OPN and associated macrophage infiltration, and in limiting AAA progression.

Fenofibrate has other effects that suggest it is likely to limit aortic aneurysm, including:

- a) *Beneficial effects on serum proteins:* Previous studies indicate that short term fenofibrate therapy reduces LDL and triglyceride serum concentrations, and increases high density lipoprotein (HDL) [39-41]. High serum HDL and low serum triglyceride levels have been negatively associated with AAA [42-44]. In addition, HDL has been demonstrated to have a range of anti-inflammatory effects, and thus the ability of fenofibrate to raise HDL and lower triglyceride could inhibit aortic inflammation and act as an additional mechanism to stabilize AAAs;
- b) *Reduced visceral fat adipokine release:* Obesity and visceral fat accumulation are risk factors for AAA, with previous data indicating that circulating adipokines, in

particular high serum resistin, are associated with human AAA [45]. Visceral adipose tissue has been suggested to be an important source of pro-inflammatory adipokines, such as resistin, and has also been implicated in promoting aortic inflammation in animal models of AAA [46, 47]. Previous studies suggest that fenofibrate can downregulate resistin production from visceral adipose tissue [46, 47]. The ability of fenofibrate to inhibit resistin production from periaortic adipose tissue could act as a further mechanism to inhibit inflammation and associated aortic destruction;

- c) *Reduced MMP-9 activity*: MMP-9 has been implicated in AAA [42, 48]. MMPs, including MMP-9 are important not only in direct extracellular matrix (ECM) degradation, but also in activating pro-inflammatory cytokines. Furthermore, MMPs have been shown to cleave OPN to a more active form [49, 50]. Data from *in vitro* studies suggest that fenofibrate inhibits MMP-9 production by vascular cells relevant to AAA progression, including macrophages and endothelial cells [51-53]. The downregulation of MMP-9 by fenofibrate would be expected to inhibit aortic destruction, in addition to limiting activation of important pro-inflammatory cytokines, such as OPN. Overall, these data suggest that fenofibrate can inhibit key pathological mechanisms involved in human AAA progression, as outlined in Fig. (1).

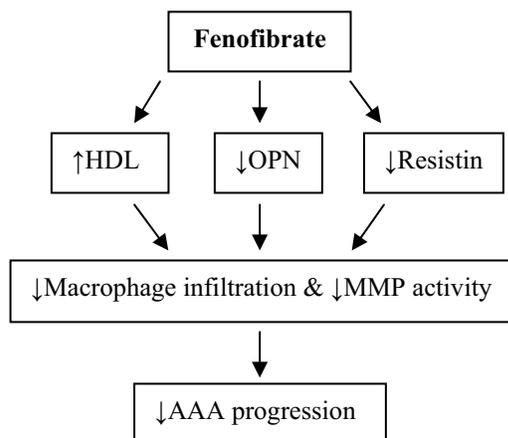


Fig. (1). Schematic illustrating the proposed mechanism by which fenofibrate reduces AAA progression.

4. FENOFIBRATE IN THE MANAGEMENT OF ABDOMINAL AORTIC ANEURYSM (FAME) AND FAME-2

FAME and FAME-2 are multi-centre, randomized, double-blind, placebo controlled trials which have recently been described in detail elsewhere [54, 55]. FAME looks to examine the effect of 145mg of fenofibrate taken daily for a minimum of 2 weeks in 42 participants scheduled for an elective open AAA repair. The primary aims are to investigate whether fenofibrate will reduce the relative number of AAA wall macrophages, reduce the relative concentration of AAA wall OPN, and reduce serum concentrations of OPN. The effect of fenofibrate on secondary parameters, including inflammatory cell number; MMPs and pro-inflammatory

cytokines within the AAA wall, periaortic fat and intramural thrombus; and circulating concentrations of AAA biomarkers including osteoprotegerin (OPG), resistin, D-dimer and fasting lipids will also be assessed. FAME-2 is a longer trial examining 24 weeks treatment with 145mg fenofibrate on key pathological markers of AAA in 140 participants with small AAAs. The primary aim is to investigate whether fenofibrate will reduce serum OPN concentration. Secondary aims include examination of the effect of fenofibrate on serum levels of resistin, lipids, MMPs and pro-inflammatory cytokines; circulating concentrations of AAA biomarkers; and AAA diameter assessed by ultrasound. Recruitment and follow-up for the FAME and FAME-2 trials is now complete with analysis underway.

5. RATIONALE FOR A DRUG TRIAL OF TELMISARTAN IN PARTICIPANTS WITH SMALL AAAs

AngII plays a central role in the regulation of blood pressure and electrolyte homeostasis, and is also capable of inducing an inflammatory response in the vascular wall [56]. In rodents, AngII stimulates the angiotensin II receptor, type 1 (AT1) to promote a series of molecular changes leading to AAA formation [57]. AngII infusion has been demonstrated to stimulate aneurysm formation in mice [11, 28, 57-59], which particularly affects the suprarenal aorta. The incidence of AAA development induced by AngII is greater in mice with similar risk factors to those associated with human AAA, such as male sex, atherosclerosis and dyslipidaemia. In these models, AAA induced by AngII is associated with increased aortic expression of pro-inflammatory cytokines, such as OPG, OPN and transforming growth factor-beta one (TGF- β 1), increased macrophage recruitment, and up-regulation of MMP-9 [57]. Experimental AAA is inhibited by activation of the nuclear receptor PPAR γ . In mice administered PPAR γ agonist over 28 days, the mean (\pm SD) suprarenal aortic diameter was reduced from 2.1 ± 0.1 mm to 1.6 ± 0.1 mm; $p=0.01$ [57]. PPAR γ activation inhibited the ability of AngII to up-regulate OPG, OPN, MMP-9 and TGF- β 1 [57].

OPG has previously been shown to stimulate an aneurysm phenotype in endothelial cells, vascular smooth muscle cells (VSMCs) and monocytes by promoting inflammation, VSMC apoptosis and release of MMP-9 [60, 61]. Furthermore, OPN- and OPG-deficient mice are relatively resistant to AAA induction by AngII [28]. OPG and TGF- β 1 stimulate up-regulation of AT1, leading to further downregulation of PPAR γ and promotion of macrophage recruitment, matrix degradation and AAA formation [57]. Together these data provide a pathway by which AngII, TGF- β 1, OPG, OPN and MMP-9 collaborate in stimulating AAA. The pathway can be interrupted using AT1 blockers and PPAR γ agonists, (Fig. 2). AT1 blockade completely abolishes the development of AAA in AngII-infused ApoE $^{-/-}$ mice [59]. Thus, AT1 is an attractive target for inhibiting the ability of AngII to promote AAA [11, 28, 58, 59]. Studies conducted using cultured human and murine cells, in addition to explants of human AAA biopsies, provide evidence that AngII binds to AT1 to promote downregulation of PPAR γ by a TGF- β 1 dependent mechanism [57]. In turn, AT1 blockade and PPAR γ activa-

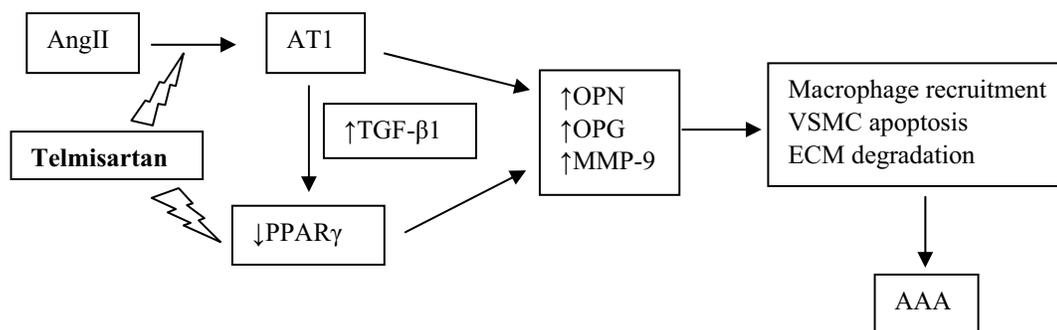


Fig. (2). Interaction between AngII, AT1, TGF- β 1, OPN, OPG and MMP-9 in AAA. This pathway can be opposed by AT1 blockade with telmisartan.

tion inhibits OPG and MMP-9 secretion by AAA explants [61].

Numerous additional findings support the importance of the AngII promoted pathological pathway. The concentration of a variety of AngII producing enzymes, including angiotensin converting enzyme (ACE), are increased in human AAA biopsies, and inhibiting these enzymes antagonizes the development of AAA in animal models [62-66]. Elevated MMP-9 has been coincidentally linked with human AAA, and deficiency of MMP-9 inhibits AAA development in mice [11, 42, 48]. Serum concentrations of OPG and OPN are elevated in participants with AAA, and are positively associated with the rate of AAA progression after adjusting for other risk factors [61, 66]. An interaction between AngII, TGF- β 1, OPG and OPN in promoting cardinal features of AAA, such as inflammation and ECM destruction, is confirmed in multiple *in vitro* and animal studies [67-70]. Importantly, AT1 blockade has been demonstrated to inhibit AAA development in three independent animal models of AAA [59, 69, 71]. Studies by other investigators also confirm that stimulation of AT1 promotes inactivation of PPAR γ [72]. The PPAR γ ligand rosiglitazone inhibits AAA formation and rupture in another mouse model [73].

Based on the data above, a medication that blocks the AT1 would appear to be an ideal therapy to reduce AAA progression. This approach is preferable to ACE inhibition for a number of reasons. For instance, unlike AT1 blockade, ACE inhibition will only indirectly inhibit the AngII pathway, and since a number of non-ACE AngII producing enzymes have been identified in human AAA biopsies [62, 66], it would only be expected to partially inhibit the progression of AAA. Also, much of the blood pressure lowering effect of ACE inhibitors appears to be due to increased circulating kinins [74]. We have previously reported that stimulation of the B2 kinin receptor promotes AAA progression and rupture in mice [75]. Telmisartan is a potent long acting AT1 blocker and also acts as a PPAR γ agonist [76, 77]. Previous data has emphasized the potential value of PPAR γ activation in limiting AAA progression [19, 73]. Telmisartan has PPAR agonist activity that is significantly greater than other AT1 blockers, in addition to its AT1 blocker actions [77, 78]. Based on this data, telmisartan would be expected to be an ideal drug to limit AAA growth.

6. TELMISARTAN IN THE MANAGEMENT OF ABDOMINAL AORTIC ANEURYSM (TEDY)

TEDY is an international multi-centre, randomized, double-blind placebo controlled trial. Participants with small AAAs will be randomized to either 40mg of telmisartan or identical placebo, daily for 24 months. The primary aim is to investigate whether telmisartan reduces AAA growth assessed by either: a) maximum diameter on ultrasound; b) maximum orthogonal diameter on computed tomography angiography (CTA); or c) maximum infrarenal aortic volume on CTA. The secondary aims are to investigate how treatment with telmisartan effects: a) circulating biomarkers for AAA progression (OPG, OPN, MMP-9, TGF- β 1 and plasma D-dimer); b) health-related quality of life; c) blood pressure; and c) requirement for AAA surgery. The TEDY study protocol has been published previously and is beyond the scope of this review [79]. Recruitment for TEDY has now concluded and the trial is expected to report in approximately 18 months.

CONCLUSION

There is no current drug therapy for AAA which has been shown to effectively limit AAA growth [20]. This mini-review describes the rationale for current trials examining the potential of the repurposed medications fenofibrate and telmisartan which are expected to report within the next 18 months. It is hoped these trials will identify a novel medication for patients with small AAAs.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Sophie E. Rowbotham and Jonathan Golledge wrote the article. All authors critically reviewed the article and approved the final version of the article.

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