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Actual Pharmacological Treatment to Reduce Growth of Small Abdominal Aneurysm

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1. Introduction

Abdominal aortic aneurysm (AAA), defined as a permanent segmental dilatation of the abdominal aorta, is a pathology responsible for significant morbidity and mortality especially among adult population over 60 years of age. Indeed, AAA is one of the fifteen most frequent causes of death among men older than 55 years in Western societies (Lederle et al., 2000). However, despite of its importance, little is known about etiopathogenesis of AAA. The observation by non-invasive imaging methods of an abdominal aorta of 3 cm typically or large in maximal diameter is generally considered to indicate aneurysm formation (Lederle et al., 2000). Diagnosis is typically made by non-invasive imaging modalities such as ultrasound, computerized tomography scan or magnetic resonance imaging with formal aortic angiography utilized in special clinical scenarios. At present, surgical treatment, conventional or endovascular surgery of AAA are very effective to prevent AAA rupture in patients with large AAA, at least 5,5 cm in diameter, with high risk of rupture. However, despite AAA with diameter <5,5 cm (termed as small AAA) have a low risk of rupture there are non well-defined therapeutic strategies for them. Moreover, the group of patients with small AAA should wait expectantly for the aneurysm reaches the minimum size to undergo surgical treatment, living through those days with great anxiety. Many factors may contribute to AAA formation and rupture, there are mechanical and rupture factors among them. Indeed, ultrasound examination showed AAA in 5.8% of World War II amputees, compared with 1% of non-amputees related to asymmetrical flow pattern at the aortic bifurcation. Moreover, evidence of genetic predisposition to the development of AAA has been noteworthy with 19% of AAA patients reporting one or more first-degree relatives with an aneurysm. Therefore, it is important to understand and know the molecular mechanisms involved in AAA expansion and which pharmacological treatments may prevent and delay it.

2. Pathophysiology of AAA

Now, knowledge of the physiopathology of AAA is necessary to understand the mechanisms of action of drugs that are being used for trying to reduce the AAA growth. Moreover, investigations are needed to design new pharmacological approaches and to

develop more effective new drugs. Although the cause of aneurismal degeneration is still non-well known, it is widely recognized that AAA are closely associated with chronic (transmural) inflammation and destruction of connective tissue proteins within the outer aortic wall. Indeed, the natural history of AAA could be summarized in three different steps. The first one is an increased production of inflammatory-related substances by the vascular wall (Figure 1). Until now, it has not been identified the triggers of this inflammatory reaction. The second step seems to be the release of molecular mediators by infiltrated cells. In addition, the third step is the release of metalloproteinases and their inhibitors in an unbalanced way mediated by the previously released inflammatory agents and infiltrated cells. Indeed, there is a reduction of the medial elastin and thinning of collagen within the media in the aortic wall .Then, it is important the role of infiltrated inflammatory cells in the degradation of the vascular wall. Indeed, activated macrophages segregate different proteases most of them members of the matrix metalloproteinase family (MMP). The increased MMP release, mainly MMP-9 and MMP-2, seem to be not compensated by an increased release of their specific inhibitors (TIMPs) (Brophy et al., 1991) favoring an unbalance between synthesis and degradation of connective tissue proteins. As mentioned before, this involves the destruction of collagen and elastin, two of the major structural components of the extracellular matrix, disrupting the orderly lamellar structure of the aortic media and then forming the aneurysm. Studies in human AAA tissue have shown extensive inflammatory infiltrates containing macrophages and lymphocytes in both the media and the adventitia. Indeed, increasing aneurysm diameter was associated with higher density of inflammatory cells in the adventitia (Freestone et al.,1995).

Fig. 1. Schematic representation of changes that occur in molecular mediators during abdominal aortic aneurysm formation.

Nowadays, the main research effort is focused on identifying new molecular pathways involved in expansion of small aneurysm. At present, drugs under investigation have been mainly designed to act on the third step of AAA formation, the inhibition of metalloproteinases system. In this regard, drugs like doxycyclins, statins and synthetic MMP inhibitors have been tested.

3. Novel drugs for AAA treatment

3.1 Doxycycline

In 1948, tetracyclines were discovered as a product of *Streptomyces aureofaciens* fermentation. Accordingly, with their origin, there are three different tetracyclines groups: natural products, semi-synthetic compounds and chemically modified tetracyclines (Nelson,1998). It is also known that tetracyclines have other effects besides the powerful antibiotic. These properties include (Sapadin & Fleischmajer,2006):

3.1.1 Inhibition of inflammation

Through the inhibition of neutrophil migration and chemotaxis, transmigration of T lymphocytes, etc (Brundula,2002;Kloppenburger,1994;Martin,1974).

3.1.2 Proteolysis

Tetracyclines and its analogues inhibit MMP (Golub,1983,1991).

3.1.3 Angiogenesis

Doxycycline inhibits MMP synthesis in endothelial cells. This inhibition promotes the decrease of both protein and mRNA MMP levels that may affect endothelial cells migration during angiogenesis (Hanemaaijer et al.,1998).

3.1.4 Apoptosis

Recent experiments have suggested antiapoptotic properties for tetracyclines (Yrjanheikki,1998,1999).

The use of tetracyclins in AAA was initially justified by the detection of microbacterial organism within the aortic aneurysm. In this regard, it has been suggested aneurysm progression associated with bacterial infection (Meijer et al.,1999). Other bacteria such as *Helicobacter pylori* and cytomegalovirus has also been linked to aortic pathology.

Tetracyclines are used as antibiotics to treat Chlamydia pneumonia-related infections but also they are non-specific inhibitors of MMPs (Ryan & Golub,2000). In this regard, AAA studies has been conducted with doxycycline. It has been shown that doxycycline decreased the protein expression of MMP-9 and MMP-2 in experimental animal models of AAA (Pyo et al.,2000). In this regard, in vitro incubation of AAA with doxycycline demonstrated inhibition of MMP-2 expression (17). It was also observed for MMP-9 production (Liu et al.,2003).

In a clinical trial, doxycycline treatment showed high tolerance and decreased MMP-9 serum levels although, did not decrease AAA size (Baxter et al.,2002). However, another clinical trial including thirty-two patients with AAA receiving doxycycline (150 mg daily) or placebo for 3 months demonstrated that AAA growth rate in doxycycline group was significantly lower than that in the placebo group (Mosorin et al.,2001).

It has been recently proposed local administration of doxycycline as a new possible therapeutic option for AAA treatment (Bartoli et al.,2006). In this regard, doxycycline administration by periaortic infusion decreased aneurysm growth as much than systemic administration of doxycycline (Bartoli et al.,2006). However in this study lower doses of local doxycycline was used with systemic doxycycline administration and, therefore, with lesser risk of adverse effects. Then, it may open the possibility to develop drug-eluting stents containing doxycycline to treat AAA.

3.2 Statins

Statins are hydroxymethylglutamyl-coenzyme A (HMG-CoA) inhibitors that are widely prescribed for their lipid-lowering effects. Although reduction of lipid levels prevents the progression of atherosclerosis, additional non-related lipid effects of statins have been also demonstrated and their have been termed as “pleiotropic statins effects”. Between the pleiotropic effects of statins may be included anti-inflammatory effects, anti-oxidant effects and reduction of MMP secretion.

Several works have demonstrated the beneficial pleiotropic effects of statins to prevent AAA development. As example, it has been demonstrated for different statins including fluvastatin, pravastatin and simvastatin, reduction of MMP-9 production by AAA and even by the infiltrated inflammatory cells (Bellosta,1998;Kalela,2001;Paraskevas,2008). In experimental studies, simvastatin increased TIMP-1 production but it did not modify inflammatory cells infiltration into AAA; however, atorvastatin suppressed macrophage recruitment by inhibiting intercellular adhesion molecule-1 expression in the vascular wall, leading to MMP-12 inhibition (Shiraya,2009;Steinmetz,2005).

It is noteworthy that in human studies, some works have not observed effects of statins on AAA growth. In this regard, there was no association between statin prescription or serum low-density lipoprotein (LDL) concentration with AAA expansion. However, AAA growth was found positively associated with initial diameter and negatively associated with diabetes (Ferguson et al.,2010). Other studies were able to find beneficial effects of statins reducing or delaying AAA expansion in humans. In this regard, Feeney et al have recently reported that prehospital statin use appears to be associated with a significant survival benefit in the ruptured AAA population (Feeney et al.,2009). In addition, an observational study including 130 patients follow up for 2 years, no aneurysm expansion was observed in 75 patients taking statins (Baxter et al.,2008). Other studies have been also suggested that the aneurysm expansion rate was decreased in the patients who were taking statins compared with those not taking statins (Schouten et al.,2006).

Another important query is about the molecular pathways by which statins may affect AAA growth. As mentioned, some studies have shown that statins reduced the in vitro expression of MMPs. However, our group using human AAA explants observed that statins particularly pravastatin, failed to modify either total production of MMP-9 or the active fraction of MMP-9 (Mateos-Cáceres et al.,2008). However, pravastatin increased TIMP-1 content in human AAA explants (Mateos-Cáceres et al.,2008). The increased TIMP-1 expression in AAA by pravastatin was unrelated to HMG-CoA inhibition by this statin (Mateos-Cáceres et al.,2008). It is remarkable that the beneficial effects of increased TIMP-1 expression may not be limited to MMP-9 inhibition. In this regard, TIMP-1 may be also involved in other cellular processes including the prevention of apoptosis which it has been demonstrated increased in AAA (Lambert,2003;Liu,2005;Zhang,2003). Accordingly, in human AAA explants pravastatin increased the expression of the proto-oncogene Bax

(associated with apoptosis induction) without modification in the expression of the anti-apoptotic proto-oncogene Bcl-2 (Mateos-Cáceres et al.,2008). However, Bax upregulation induced by pravastatin did not modify Bax/Bcl-2 ratio, an important apoptotic index, probably discarding that pravastatin may influence apoptotic status in AAA. Therefore, it is plausible that TIMP-1 may be involved in other biological functions such as growth factor-like activity, stimulation of aortic smooth cell proliferation and anti-inflammatory activity, which may all prevent AAA progression.

In summary, statins may be useful in controlling AAA growth, although the exact involved molecular mechanisms remained to be elucidated. However, many studies promote an pleiotropic effect of statins to prevent AAA growth which seem to be associated with reduction of inflammation in the aneurysmal wall, in addition to diminish MMP expression and/or enhance the synthesis of their inhibitors, TIMPs.

3.3 Synthetic inhibitors of MMPs

MMPs play a fundamental role in the development of aneurysm. Therefore, it is then plausible that the use of synthetic inhibitors may slow AAA growth. BB-94 (Batimastat) is a broad-spectrum inhibitor of metalloproteinases that has been effective in controlling inflammatory responses in rats (Rassmussen,1997;Taraboletti,1995).

BB-94 decreased the aneurysm expansion in rats (Bigatel et al.,1999). Researchers have also observed that BB-94 has effect not only as metalloproteinases inhibitor but also decreasing the inflammatory response to aneurysm. However, long-term used of BB-94 is at present limited by its lack of bioavailability. Marimastat, a second generation of this type of drugs, it is active orally but it has been demonstrated 30% of musculoskeletal side effects. It has been studied in human experimental models of intima hyperplasia and aneurysms (Porter et al.,1998). These initially promising drugs have failed to show human therapeutic utility, and other drugs have overlooked them.

3.4 Angiotensin Converting Enzyme Inhibitors (ACEI) and angiotensin receptor blockers

ACEI are drugs used for blood pressure control. Several studies have shown that ACEI affect the natural evolution of aneurysms although their possible mechanisms of action are not well known. It has been observed that administration of Angiotensin-II to experimental animals decreased the content of elastin in the aortic wall including in AAA (Tham et al.,2002). Moreover, ACEI administration to patients with established AAA increased collagen production in the vascular wall and decreased the arterial wall size (Claridge et al.,2004). Liao et al demonstrated that different ACEI could decreased elastin in AAA independently of their lowering arterial blood pressure effects and without changes in the inflammatory status of the aortic wall (Liao et al.,2001). Moreover, Alsac et al. have shown that perindopril, an ACEI, is able to reduce aneurysm growth in experimental models not only by changes in elastin levels but also by inhibiting MMPs synthesis (Alsac et al.,2011). In clinical trials, patients treated with ACEI before inclusion presented lesser aneurysm rupture than those not treated with ACEI. This effect was not observed in patients treated with other blood pressure lowering drugs including β -blockers, calcium channel blockers antagonists of angiotensin-II receptors and even diuretics (Hackam et al.,2006).

However, there are also studies demonstrating detrimental effects of ACEI on AAA growth. For example, a study performed with 1700 patients from UK showed that aneurysm growth

rate was higher in patients treated with ACEI compared with those without ACEI treatment (Sweeting et al.,2010). These findings support that are needed prospective randomized studies to clarify the real therapeutic benefits of ACEI for AAA.

There are also studies testing the effect of angiotensin II-receptor antagonists (ARBs) to prevent AAA growth. In experimental models based on the chronic release of angiotensin II into apolipoprotein deficient mice resulted in aortic dilation and eventual rupture, losartan administration prevented aneurysm formation (Fujiwara et al.,2008). Moreover, antagonism by losartan of transforming growth factor-B prevented progressive matrix degradation (Habashi et al.,2006). More studies, particularly clinical studies, are needed to assess the utility of ARBs to prevent AAA growth.

4. Conclusions

The study of AAA should be focused on the knowledge about the main causes that produces the inflammatory infiltrate resulting in the cascade of events that ends with aneurysm formation. Moreover, it is also important to delay AAA growth. In this regard, reduction in the expansion rate of AAA potentially increases the time of surgical intervention and in many cases, this delayed time may exceed life expectation for patients.

Larger multicenter studies are needed to fully elucidate the effect of the currently used drugs. Moreover, it is important the efforts in the research of this disease, focusing in the determination of mechanisms involved in the appearance of the inflammatory infiltrate. In this regard, protein expression studies may help us to identify new molecular mediators and pathways including oxidative-stress mediators, energetic metabolism targets and others involved in AAA formation and growth. This type of studies may open new knowledge about the disease, in addition to find new molecular targets to develop drugs and pharmacological treatments.

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This book considers mainly diagnosis, screening, surveillance and treatment of abdominal, thoracoabdominal and thoracic aortic aneurysms. It addresses vascular and cardiothoracic surgeons and interventional radiologists, but also anyone engaged in vascular medicine. The high mortality of ruptured aneurysms certainly favors the recommendation of prophylactic repair of asymptomatic aortic aneurysms (AA) and therewith a generous screening. However, the comorbidities of these patients and their age have to be kept in mind if the efficacy and cost effectiveness of screening and prophylactic surgery should not be overestimated. The treatment recommendations which will be outlined here, have to regard on the one hand the natural course of the disease, the risk of rupture, and the life expectancy of the patient, and on the other hand the morbidity and mortality of the prophylactic surgical intervention. The book describes perioperative mortality after endovascular and open repair of AA, long-term outcome after repair, and the cost-effectiveness of treatment.

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