Published in final edited form as:

Expert Opin Pharmacother. 2010 February ; 11(2): 207–213. doi:10.1517/14656560903439737.

Pharmacotherapy for End-stage Coronary Artery Disease

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Abstract

Importance of the field—Coronary artery disease remains the leading cause of mortality in the industrialized world. Despite advances in surgical and catheter based interventions, a select number of patients remain with no options for invasive therapy. The goal of this review is to discuss the current status of pharmacotherapeutic interventions to treat end stage coronary artery disease.

Areas covered in this review—Literature review on the topic of therapeutic angiogenesis from 1980 – 2009.

What the reader will gain—Insight into current therapeutic strategies employed to manage end-stage coronary artery disease.

Take home message—Multiple strategies to manage end-stage coronary disease are under investigation. The most promising of these approaches focuses on augmenting the endogenous angiogenic response to chronic myocardial ischemia via utilization of growth factors.

Keywords

Angiogenesis; Coronary Artery Disease; Growth Factors; Myocardial Ischemia

1. INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of mortality in the industrialized world [1]. Despite advances in screening, lifestyle modification, medical therapy and surgical intervention, the prevalence of CAD and the associated mortality and morbidity remain widespread.

A significant subset of patients with advanced CAD suffer from disease which is not amenable to surgical or percutaneous revascularization, or undergo incomplete revascularization secondary to a lack of adequate distal bypass targets and small vessel disease [2]. These patients, who suffer from “end-stage” CAD, represent a population in whom pharmacotherapeutic strategies must be refined in order to provide treatment. Central to the

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Declaration of interest

N R Sodha is supported by National Institutes of Health grant T-32HL076130-02 and the Irving Bard Memorial Fellowship. F W Sellke is supported by RO1 HL69024 and RO1 HL46716. L M Chu is supported by the Irving Bard Memorial Fellowship. M Boodhwani is supported by National Institutes of Health grant HL04095-06 and the Irving Bard Memorial Fellowship.

development of these strategies lies the process of angiogenesis. The body's endogenous response to chronic myocardial ischemia results in the development of collateral vessel formation to restore some degree of perfusion to the ischemic tissue. In most cases, this response is inadequate to normalize perfusion to myocardium distal to an occluded or significantly blocked coronary artery. Augmentation of this response via the utilization of various pharmacologic agents has been termed "therapeutic angiogenesis". These therapies have generally focused on the utilization of gene and protein based growth factor therapy, as well as revisiting medications which have been found to have pleiotropic effects beyond their initial applications such as hormones, nitric oxide donors, and statins. The focus of this review is to highlight the current status of these agents in the setting of therapeutic angiogenesis.

2. GROWTH FACTORS

The primary growth factors utilized in large animal and human trials of therapeutic angiogenesis include vascular endothelial growth factors (VEGF), and members of the fibroblast growth factor (FGF) family. Growth factors in the VEGF family function as mitogens for endothelial cells and stimulate endothelial progenitor cell (EPC) mobilization from bone marrow [3]. When initially evaluated in large animal models of chronic myocardial ischemia, local delivery of VEGF to ischemic myocardium resulted in significant improvements in myocardial perfusion [4,5].

Members of the FGF family induce endothelial cell proliferation, survival, and differentiation, as well as migration of multiple cell types involved in vascular formation [6]. As with VEGF, large animal studies of chronically ischemic myocardium demonstrated significant improvements in myocardial perfusion after local delivery of FGF [7,8].

Phase I clinical trials conducted in the 1990's demonstrated the safety of intra-myocardial delivery of FGF, as well as benefit in myocardial perfusion and left ventricular function [9, 10]. Subsequent phase II trials demonstrated intra-myocardial delivery of FGF resulted in reductions in perfusion defects relative to placebo treated patients. Phase I clinical trials evaluating VEGF therapy demonstrated the safety of intra-vascular delivery of VEGF, and some improvement in myocardial perfusion [11–13].

Despite the promising results of the large animal and phase I clinical trials, subsequent larger phase II trials failed to yield such positive results. A multi-center, randomized, double-blinded placebo controlled clinical trial involving 178 patients to receive VEGF (high or low dose) vs. placebo via intra-coronary infusion followed by intravenous infusions demonstrated no significant functional benefit relative to placebo [14].

A phase II trial investigating FGF delivered via an intra-coronary route in patients unable to receive percutaneous or surgical revascularization demonstrated a decrease in angina frequency in treated patients at 90 days, but this benefit was lost at 180 days [15].

The cause for markedly positive animal experiments and largely negative clinical trials are uncertain, but may involve a discrepancy in the relatively young, otherwise healthy animal models used and the patients enrolled in clinical trials, who all have advanced endothelial dysfunction and risk factors for coronary disease such as diabetes, hypercholesterolemia and hypertension. These risk factors have been associated with a reduced capacity for endogenous collateral development [16,17] and angiogenic therapy using growth factors [18,19]. Gene therapy trials, in which a gene encoding an angiogenic growth factor is delivered, have not had much more success. For example, in the AGENT trial, FGF-4 gene delivered via an adenoviral vector resulted in no significant difference in exercise treadmill time at 4 or 12 weeks or other objective or subjective improvement in perfusion [20]. In the NORTHERN trial, a randomized, double-blinded, placebo controlled study comparing VEGF165 plasmid to placebo, there was

no difference between the groups at 3 or 6 months when comparing perfusion, size of ischemic area, exercise treadmill time, or anginal symptoms, though the ischemic area, exercise time, and anginal symptoms were similarly improved in both groups [21]. A strong placebo effect is well documented in angiogenic trials [22]. Thus, angiogenic therapy, whether it is using growth factors or genes encoding the growth factors, has not had a substantial impact on the treatment of patients with coronary artery disease to date. A better understanding of the science behind collateral formation and what inhibitory factors prevent angiogenesis in patients will be required before clinical trials will show a benefit of therapy.

3. THYROID HORMONES

Hypothyroidism has been associated with the development of CAD, and many patients with CAD have been found to have subclinical hypothyroidism on serum assays [23]. Thyroid hormone supplementation has previously been shown to augment myocardial function [24] and induce vasodilatation [25]. While some of these effects are related to metabolic stimulation provided by exogenous thyroid hormone supplementation, of greater interest has been the demonstration of arteriolar growth and stimulation of angiogenesis in normal myocardium with thyroxine supplementation. In the post-infarcted myocardium, thyroid hormone analog supplementation has been shown to induce angiogenesis [26]. The thyroid hormone analog DITPA (3,5-diiodothyropropionic acid) can promote a healthy coronary vasculature (prevent arteriolar loss) independently from its thyroid effects on cardiac function [27]. Thyroid hormones and DITPA can stimulate angiogenesis in normal animals [28,29] and in myocardial infarction models [30]. The mechanism underlying the pro-angiogenic effects of thyroid hormone supplementation remain to be elucidated. While the direct pathway is unknown, the stimulation of pro-angiogenic signaling proteins such as VEGF, bFGF, angiopoietin-1, and Tie-2 with thyroid hormone supplementation provides support to an underlying link between the two [29].

The pre-clinical studies identifying thyroid hormone supplementation as a potential pro-angiogenic agent have been met with some concern given the potential adverse effects on metabolism and myocardial oxygen demand. The only clinical trial examining thyroid hormone supplementation in cardiovascular disease was terminated secondary to body mass loss in the treated subjects [31].

4. ERYTHROPOIETIN

Erythropoietin, an endogenous erythropoietic hormone, has been shown to have multiple pleiotropic effects in addition to its effects on red blood cell production [32,33]. While the studies to date examining the angiogenic effects of erythropoietin have been limited to murine models, erythropoietin has been shown to have a stimulatory effect on the production of endothelial progenitor cells (EPCs) [34] which are involved in neovascularization of ischemic tissues [35,36]. Erythropoietin therapy also enhanced angiogenesis in peri-infarcted myocardium after MI in rats [37]. When applied topically via gelatin sheets to infarcted myocardium, erythropoietin therapy resulted in increased microvascular density relative to saline. Interestingly, the effects of erythropoietin seem to be independent of an increase in red cell mass [38]. Ongoing clinical trials such as the HEBE III trial, a prospective randomized controlled study on the effects of a single bolus of erythropoietin on left ventricular ejection fraction and infarct size after percutaneous coronary intervention for first-time MI, promise to further elucidate the safety and clinical efficacy of erythropoietin in the treatment of CAD [39].

5. SODIUM NITRITE

Nitric oxide (NO) acts as a key signaling molecule for the stimulation of angiogenesis [40], specifically in VEGF mediated angiogenesis [41]. These findings led to investigation into NO donors as potential therapeutic agents to augment myocardial angiogenesis in the setting of chronic ischemia [42,43]. While a seemingly attractive approach, the majority of NO donors are non-selective and may in fact induce cellular injury [44]. Nitrite, on the other hand, can act as a selective NO donor as it can be reduced back to NO by multiple mechanisms. These findings have led to recent investigation into the therapeutic utility of chronic nitrite therapy to augment angiogenesis. While investigation utilizing nitrite therapy in the myocardium is lacking, Kumar and colleagues have recently demonstrated that chronic administration of sodium nitrite to mice with ischemic hind limbs resulted in a significant improvement in endothelial cell density and tissue blood flow to ischemic areas. Interestingly, nitrite was found to accumulate preferentially in ischemic tissues [45]. While the results of this study are quite interesting, further investigation is necessary to determine applicability to the myocardium.

6. L-ARGININE

As discussed above, NO is essential to the angiogenic signaling cascade. L-arginine is a substrate for endothelial nitric oxide synthase (eNOS) and is metabolized into NO. Large animal studies have demonstrated oral supplementation with L-arginine improves collateral formation in the setting of chronic myocardial ischemia [46], and in addition augments collateral dependent perfusion when utilized in conjunction with VEGF [47] or FGF-2 [48]. When evaluated in clinical trials, patients randomized to receive L-arginine versus placebo after acute myocardial infarction actually demonstrated increased mortality (8.6 % in L-arginine group vs 0% in placebo at 6 months) [49]. These findings are discordant with the results of a smaller trial evaluating the effects of L-arginine supplementation with or without VEGF DNA in patients undergoing coronary artery bypass grafting which demonstrated trends towards smaller perfusion defects in the combination therapy subset [50].

7. PLASMINOGEN ACTIVATOR

Central to the initiation of angiogenesis lies vessel destabilization to allow for new vessel formation [51]. Plasminogen activators are essential to this process, allowing for basement membrane degradation and activation of matrix metalloproteases [52]. Urinary Plasminogen Activator (uPa) stimulates endothelial cell tube formation on fibrin matrices [53]. From a therapeutic perspective, plasmid based uPa over-expression has been shown to stimulate vessel growth and improve tissue perfusion in myocardium subjected to ischemia in a murine model. These functional outcomes were associated with increases in capillary density and smooth muscle containing arterioles, without any observed effects on non-ischemic myocardium [54].

8. STATINS

Statins, potent inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, are known to have pleiotropic effects beyond their lipid lowering capabilities. While data demonstrating a clinical benefit of statin therapy is abundant, reports as to the effects of statins on myocardial angiogenesis have been conflicting. In vitro studies have demonstrated statins are able to promote angiogenesis in human umbilical vein endothelial cell models, but may also be associated with decreased endothelial cell tube formation [55]. These discrepant findings seem to be dose dependent, with high-dose statin therapy attenuating the angiogenic response [56]. Porcine models of chronic myocardial ischemia have demonstrated that statins aid in improving endothelial function which is essential to the angiogenic process, but may be associated with impaired formation of functional coronary collaterals [57,58], possibly

secondary to increased myocardial oxidative stress [59]. While there have been no clinical trials to assess the efficacy of statin therapy in improving the myocardial angiogenic response to chronic ischemia, patient studies have again demonstrated discrepant results with one study demonstrating enhanced coronary collateralization with statin therapy [60], and another showing absence of any benefit [61].

9. CONCLUSION

End-stage disease afflicts a significant number of patients with CAD. In this group of patients with no options for coronary revascularization, therapeutic angiogenesis presents an attractive option. Unfortunately, current agents in use have met with little clinical success. The most promising of these strategies may lie with the use of pro-angiogenic growth factors, but additional studies are needed to delineate the gap between the results of pre-clinical and clinical trials.

10. EXPERT OPINION

The clinical need for new therapeutic strategies for the management of end-stage CAD remains clear. While coronary interventions, whether via percutaneous transluminal coronary angioplasty, coronary artery stenting, or coronary artery bypass grafting remain the mainstay of therapy for patients with advanced CAD, the significant subset of patients who are not candidates for such procedures represent a large patient population in whom therapeutic angiogenesis remains a promising treatment modality. Currently investigation has focused on agents in clinical use for alternative indications which are now known to have pleiotropic effects as well as agents specifically developed to augment the angiogenic response to chronic myocardial ischemia. The therapeutic efficacy of thyroid hormones has been demonstrated in several small animal models, but the lack of large animal studies, as well as the detrimental metabolic effects of thyroid hormone supplementation leave a large gap between current research and applicability to patients. Similar caution is raised when evaluating plasminogen activators for therapeutic use given the limited number of experimental studies demonstrating its efficacy. Interestingly, the results of studies by Traktuev et al [54] were notable for the possible synergistic effects of uPA in combination with VEGF. While statins have been the focus of extensive investigation in both laboratory and clinical studies and found to be generally safe, their effects on the angiogenic process remain unclear. Data are conflicting regarding the augmentation or inhibition of collateral formation in myocardium. While the clinical benefits of statin therapy are well-established for management of hyperlipidemia, the application of statin therapy to improve coronary collateral formation will require further studies. Cell based therapy using endothelial progenitor cells, myoblasts or other stem cells to improve myocardial function and perfusion has recently received much attention and is the subject of intense investigation. However, nearly all trials to date have been negative or nearly so, despite the conclusions proposed by some of the investigators. A randomized, controlled trial investigating intracoronary injection of autologous bone marrow cells after acute ST-elevation MI revealed no difference in left ventricular function compared to the control group [62], while two slightly larger trials demonstrated only small but significant improvements in left ventricular function in response to transcatheter treatment with bone marrow- and blood-derived progenitor cells [63,64]. Cell therapy is subject to many of the same limitations as gene therapy or growth factor therapy. In addition, cell therapy has limitations with cell delivery, survival and engraftment.

It is our belief the most promising strategy to improve coronary collateral circulation in patients with end-stage CAD remains growth factor therapy. As detailed above, therapeutic angiogenesis utilizing members of the VEGF and FGF family has been shown to be efficacious on a molecular, histologic, and functional level in large animal studies of chronic myocardial ischemia. These findings have led to multiple clinical studies which have demonstrated the

safety of growth factor therapy. While data are lacking to demonstrate a significant objective benefit in patient studies, current research delineating the molecular pathways underlying the angiogenic process has provided exciting targets to augment growth-factor therapy. These include agents to reduce the oxidative stress burden associated with CAD, molecular targets to inhibit the expression of anti-angiogenic proteins, as well as agents to promote NO signaling. The combination of excellent pre-clinical results, demonstrated safety in patient studies, and rapid delineation of novel targets to augment therapeutic angiogenesis utilizing growth factors provides a degree of enthusiasm for further investigation in to this area.

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