SY 1/1 NEW PHARMACOTHERAPIES IN ISCHEMIC HEART DISEASE: ANGIOGENESIS AND PHARMACOGENOMICS

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Angiogenesis in ischemic heart disease

More than 6 millions world population died from ischemic heart disease in 1990 (1). It remains the leading cause of morbidity and mortality worldwide beyond 2000. The improvements in survival of patients with acute myocardial infarction, mainly by coronary reperfusion and revascularization interventions, and of the aging population cause increasing the numbers of patients who suffered from chronic myocardial ischemia. Many of them are not candidates for any conventional revascularization treatments including coronary artery bypass graft surgery and percutaneous coronary intervention (2). These patients comprised 5-15% of patients underwent coronary angiography. New treatment modalities for myocardial ischemia has been recently developed and one of these most promising interventions is therapeutic angiogenesis.

Angiogenesis is the growing of new collateral vessels from pre-existing blood vessels. It is one of the processes for developing coronary collateral circulation which provide perfusion to ischemic myocardium. The new therapies for ischemic heart disease to enhance angiogenesis are therapeutic angiogenesis by gene or angiogenic growth factors therapy to stimulate the growth of collateral vessels and transmyocardial or direct myocardial revascularization (TMR or DMR) using lasers to punch holes in the myocardium and promote channels or induce collateral circulation.

Many angiogenic growth factors have been demonstrated to generate angiogenesis in animal models; however, only vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) have been focused on recent clinical trial in ischemic heart disease. Intramyocardial, intracoronary, intrapericardial or intravenous administration of VEGF-A, VEGF-C or FGF-2, FGF-4 genes (naked DNA, plasmid-liposome complexes, adenovirus mediated gene tranfer systems) or recombinant proteins (VEGF or b-FGF; FGF-2) in myocardial ischemia patients has resulted in successful therapeutic angiogenesis (3-6). The 3-yr follow-up after intramyocardial injection of human FGF in ischemic myocardium showed an increase in left ventricular ejection fraction and improvement in clinical appearance (7). However the first randomized controlled study :VEGF in Ischemic for Vascular Angiogenesis (VIVA) trial has not demonstrated clinical benefit (8). Recent trial on direct myocardial injection of VEGF gene in chronic myocardial ischemia patients who refractory to conventional treatments showed improvement of ischemia by clinical and perfusion scan studies. The average ischemic area decreased from 6.45 ± 1.37 to 0.95 ± 0.41 cm^2 at day 60 after therapy ($p = 0.001$). The numbers of angina free patients increased from 0 to 62%, the angina episodes decreased from 48.1 ± 4.9 to 2.0 ± 0.8 episodes per week after 180 days of gene therapy ($p < 0.0001$) (9).

One of the major concerns on growth factors therapy in human is the possible increase risk of malignancy, or proliferative retinopathy especially in diabetic patients.

Therefore all patients eligible for angiogenesis trial must have no evidence of malignancy, renal insufficiency or proliferative retinopathy and so far there is no report of such complications in the patients after the therapy. However the long term efficacy and safety of this new intervention still have to be close monitored.

In canine model of chronic ischemia, transmyocardial laser revascularization (TMLR) significantly enhances angiogenesis and increased blood flow capacity during stress.(10) The results of clinical trials on TMLR either by surgical or percutaneous procedures has been controversial (11-13) related to the disproportion of symptoms and myocardial perfusion improvement, placebo effect and the unproven mechanism of action. However TMR using holmium:yttrium-aluminium-garnet (YAG) and carbon dioxide lasers has been recently approved by the United States Food and Drug Administration for the treatment of medically refractory angina in patients without conventional options (14).

Despite the promising early clinical results, there are still so many questions to be answered before therapeutic angiogenesis and TMR can be prescribed for ischemic heart disease patients. These unresolved issues are the biology of angiogenesis, the selection of appropriate patients, choice of end points and means of assessments (clinical outcome or coronary angiographic study or perfusion scan etc.), choice of treatment strategy (gene or protein, which gene or peptide, naked DNA or liposome or viral vector), route of administration (intracoronary or intravascular or intramyocardium) and side effect profile. The large-scale clinical trails are needed to validate these therapies which will be the new way for refractory coronary ischemic syndrome treatment in the near future.

Pharmacogenomics in cardiovascular disease:

Thanks to Human Genome Project that accelerate the progression of population genetics and polymorphism. The numbers of publications indexed in MEDLINE which related to genetic polymorphism were more than 6000 in the year 2000. These gave rise to the increase important in clinical practice of "pharmacogenomics". Pharmacogenomics are the studies of molecular and genetic factors that determine drug efficacy and toxicity. The response of drug in each individual is depended on the heterogeneity of pharmacokinetic and pharmacodynamic determined by genetic polymorphism. For example, heart failure patients who carried the *ACE* gene polymorphism of *DD* genotype had a significantly better event-free survival when treated with beta-blockers than those not received therapy ($p = 0.007$) but the *II* and *ID* genotype patients did not show these survival benefit with beta-blockers(15). Regarding adverse drug reaction (ADR), pharmacogenomics also play an important future role: for example, CYP2C19 polymorphism that produced the poor metabolizer in 16-23% of Chinese and Japanese people may determine the ADR of isoniazid in Asian population, CYP2C9 polymorphism which associated with lower CYP2C9 enzyme may increase the prevalence of warfarin overdose ADR (16). In the near future, we may have to screen for genotype of certain gene to determine the most appropriate drug with the most effective and least ADR for each individual.

References:

1. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. Lancet 1997;349:1269-76.
2. Henry TD. Therapeutic angiogenesis. BMJ 1999; 318: 1536-9.
3. Schumacher MD, Pecher MD, von Sprecht BU, Stegmann T. Induction neoangiogenesis in ischemic myocardium by human growth factors: clinical results of a new treatment of coronary heart disease. Circulation 1998;97:645-50.
4. Sellke FW, Laham RJ, Edelman ER, Pearlman JD, Simons M. Therapeutic angiogenesis with basic fibroblast growth factor: technique and results. Ann Thorac Surg 1998;65:1540-4.
5. Henry TD, Singh RK, Isner JM, Kereiakes DJ, Giordano FJ, Simons M, et al. Results of intracoronary recombinant human vascular endothelial growth factor (rhVEFG) administration trial. J Am Coll Cardiol 1998;31:65A.
6. Losordo DW, Vale PR, Symes JF, et al. Gene therapy for myocardial angiogenesis: initial clinical with direct myocardial injection of phVEGF165 as sole therapy myocardial ischemia. Circulation 1998;98:2800-4.
7. Peter P, and Schumacher BA. Angiogenesis in ischemic human myocardium: Clinical Results After 3 Years. Ann Thorac Surg 2000;69:1414 -9.
8. Henry, T.D. et al. Double blind, placebo controlled, trial of recombinant human vascular endothelial growth factor: the VIVA trial. J Am Coll Cardiol. 33, 384A 874 (1999).
9. Vale PR, Losordo DW, Milliken CE, Maysky M, Esakof DD, Symes JF, Isner JM. Left ventricular electromechanical mapping to assess efficacy of phVEGF165 gene transfer for therapeutic angiogenesis in chronic myocardial ischemia. Circulation. 2000;102:965-974.
10. Yamamoto N, Kohmoto T, Gu A, DeRosa C, Smith CR, Burkhoff D. Angiogenesis is enhanced in ischemic canine myocardium by transmyocardial laser revascularization. J Am Coll Cardiol. 1998;31: 1426–33.
11. Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial. Lancet 1999;353:519-24.
12. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med 1999;341:1029-36.
13. Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. N Engl J Med 1999;341:1021-8.
14. Allen KB, Shaar CJ.Transmyocardial laser revascularization: surgical experience overview. Semin Interv Cardiol 2000 Jun;5(2):75-81.
15. McNamara DM, Holubkov R, Janosko K, Palmer A, Wang JJ, MacGowan GA, Murali S, Rosenblum WD, London B, Feldman AM. Pharmacogenetic interactions between β- blocker therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure Circulation. 2001;103:1644-1648.
16. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions. JAMA 2001;286:2270-279.