Journal of Clinical Trials
ISSN: 2167-0870

Meng et al., J Clin Trials 2017, 7:4
DOI: 10.4172/2167-0870.1000322

Research Article Open Access

Safety and Efficacy of Intracoronary Ad-HGF Administration for Treating Severe Coronary Disease: Results From Long-Term Follow-Up of a Phase I Clinical Trial

Haoyu Meng, Yingqiang Du, Bo Chen, Mohammad Bilaal Toorabally, Ze-Mu Wang, Ningtian Zhou, Zhihui Xu, Dingguo Zhang, Zhengxian Tao, Liansheng Wang, Qingzhe Jia* and Zhejean Young*

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing, 210029, China

Corresponding author: *Qingzhe Jia, Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing, 210029, China, E-mail: qzjiadoc@163.com*

Zhejean Young, Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing, 210029, China, Tel: 86 25 68136076; E-mail: zhijianyangnj@njmu.edu.cn

Received date: July 24, 2017; **Accepted date:** August 14, 2017; **Published date:** August 16, 2017

Abstract

Objective: This study is a long-term follow-up of our previous phase I clinical trial and aims at evaluating the long-term safety and efficacy of intracoronary Ad-HGF administration for treating coronary disease.

Methods: This study includes 22 patients (11 in the experiment group and 11 in the control group) with diffused and severe coronary disease who had received the optimal standardized medication therapy and was not amenable to revascularization. Intracoronary Ad-HGF gene transfer was administered to the distal part of the accessible artery by over-the wire balloon or at the ostium of the target vessels by diagnostic coronary catheter in the experiment group. Safety parameters were measured and compared between baseline and follow-ups (5-week; 12-month; 36-month) only in the experiment group. The changes of efficacy parameters (ejection fraction, EF) from baseline to 36-month follow-up (δEF) were measured in both groups and compared with each other.

Results: This study confirmed the long-term safety of intracoronary Ad-HGF administration for treating severe diffuse coronary disease. All the eleven patients of the experiment group were alive after 36-months follow-up. During the follow-up, no new-onset arrhythmia was recorded; no malignant tumor was diagnosed; no paroxysmal or long-term fever was recorded; no retinal vascular anomaly was diagnosed. There were no statistically significant differences between the follow-ups and baseline in regard to blood parameters, including WBC, Hb, ALT, AST, BUN, Cr, CEA and AFP. In addition, intracoronary Ad-HGF efficiently improved echocardiographic EF at the 36-month follow-up compared to baseline (F=4.4, p=0.024) and with the control group (δEF: 3.5 ± 1.1 *vs.* -4.5 ± 1.3, MD: 8, p=0.0001). The medium-high dose subgroup also showed higher ECT-EF at the 36-month follow-up than baseline (MD: 4.8, p=0.017, n=8) and higher improvement of ECT-EF than the control group (δEF: 4.8 ± 1.5 *vs.* 0.3 ± 1.7, MD: 4.5, p=0.08).

Conclusion: Intracoronary Ad-HGF administration is safe and potentially efficient in improving EF of patients with severe diffuse coronary disease in 3-year follow-up.

Keywords: Gene therapy; Hepatocyte growth factor; Angiogenesis; Coronary disease

Introduction

As a pluripotent growth factor, hepatocyte growth factor (HGF) has been proved to have potent angiogenic, anti-inflammatory, anti-fibrotic, and anti-apoptotic effects which can be beneficial for various types of ischemic tissues especially in myocardial infarction and ischemic heart failure [1-5]. Previously, we engineered a replication-deficient adenovirus that carries the HGF gene (Ad-HGF). It mediated high expression of HGF to increase the number of functional arterioles and improve the growth of collateral circulation [6]. In several ischemia animal models, Ad-HGF gene transfer proved to have efficient angiogenesis effects without apparent toxicity and mutation [7,8]. Our preceding phase I clinical study demonstrated the short-term safety of direct intracoronary administration of Ad-HGF to treat severe coronary disease, which showed that in the acute phase, up to day 35, there were no serious adverse events [9]. This study is a long-term follow-up of our prior phase I clinical trial. It evaluates the long-term safety and efficacy of intracoronary Ad-HGF administration for treating severe diffuse coronary disease.

Materials and Methods

Study design

This study was performed in the Department of Cardiology at the First Affiliated Hospital of Nanjing Medical University, which was approved by the Ethical Committee of the hospital and the State Food and Drug Administration of China (ref. 2005L01181). The written consents were obtained from all patients. Each patient received the optimal standardized medication therapy for coronary disease including aspirin or clopidogrel, beta blockers, statins, angiotensin

conversion enzyme inhibitors or angiotensin II receptor blockers, and was treated with Ad-HGF only once (constructed and produced by Chinese Academy of Military Medical Sciences) [9-12]. Inclusion criteria for the intracoronary gene transfer were 50-80 years old with Canadian Cardiovascular Society class II to III angina, suffered from diffused and severe coronary disease confirmed by coronary angiography, the main coronaries not amenable to interventional therapy (angioplasty or stenting) or bypassing grafting, and no emergency revascularization during follow-ups. Patients were excluded if they had malignancy, kidney failure, hepatic failure, acute myocardial infarction or received emergency revascularization.

In our previous phase I clinical trial, there were 18 patients assigned to three groups according to the dosage of Ad-HGF (5*109 pfu, 1*1010 pfu, or 2*1010 pfu), and each group had six patients, seven patients were excluded since they received revascularization during follow-ups. Finally, 11 patients were included in the experiment group of this study (three in 5*109 pfu group, four in 1*1010 pfu group, and four in 2*1010 pfu group) (Table 1).

Parameter	Experiment group			Control group	F	P
	5*109 pfu	1*1010 pfu	2*1010 pfu			
N	3	4	4	11	-	-
Male	2	4	4	8	-	-
Age, years	64 ± 8.9	61.5 ± 8.2	62.5 ± 8.8	61.6 ± 10	0.06	0.98
Risk factor						>0.05
Hypertension	2	2	3	8	-	
Diabetes	2	3	3	7	-	
Smoking	1	2	1	6	-	
Medications						>0.05
Aspirin/ Clopidogrel	3	4	4	11	-	
Statin	3	4	4	11	-	
ACEI/ARB	3	3	4	11	-	
β- blocker	3	4	3	11	-	

ACEI: Angiotensin Conversion Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers

Table 1: Characteristics of the 22 patients included in the study.

Gene transfer

Coronary angiography was performed *via* the femoral artery according to standard procedures. Based on the previous study [9,10], Ad-HGF gene was transferred to the distal part of the accessible artery by over-the wire balloon. If the vessel could not be reached, the procedure was performed by diagnostic coronary catheter at the ostium of the target vessels [9,10]. Ad-HGF was diluted to 2 ml with normal saline and then injected within 30 sec, followed by flushing of the catheter with normal saline. Coronary angiograms were obtained at the end of each infusion [9,10].

Safety parameters

The safety parameters including death, acute myocardial infarction, acute stroke, new-onset arrhythmia, malignant tumor and paroxysmal or long-term fever, retinal vascular anomaly, as well as several blood parameters including white blood cell count (WBC), hemoglobin (Hb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), serum urea nitrogen (BUN), carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) were measured at baseline and during follow-ups in the experiment group.

Efficacy parameters

The efficacy parameters including echocardiographic ejection fraction (EF) and EF of cardiac Emission Computed Tomography (ECT-EF) were measured at baseline and 36-month follow-up in both groups.

Statistical analysis

Stata 10.1 was used for statistical analysis. Repeat measured ANOVA was performed to evaluate the difference in safety parameters between baseline and follow-ups. Paired t test was performed to evaluate the mean difference of changes in EF (baseline to follow-up) between experiment group and control group. The results are presented as mean difference (MD) ± standard deviation and $P<0.05$ was considered statistically significant.

Results

Clinical characteristics

Characteristics of the recruited 22 patients are shown in Table 1, and there were no significant difference between groups.

Safety parameters

All the eleven patients of the experiment group were alive after 36-months follow-up. One patient suffered from an acute stroke in the 7th month post-procedure. It was regarded as a serious adverse event but was not directly related to the treatment. During the follow-up, no new-onset arrhythmia was recorded; no malignant tumor was diagnosed; no paroxysmal or long-term fever was recorded; no retinal vascular anomaly was diagnosed.

There were no statistically significant differences between the follow-ups (5-week, 12-month or 36-month) and baseline in regard to blood parameters, including WBC, Hb, ALT, AST, BUN, Cr, CEA and AFP (Table 2). This indicated that there were no significant hematocytopenia, tumor biomarkers, liver function and renal function abnormalities during the follow-up.

Efficacy parameters

In the experiment group, the 36-months follow-up revealed a significant higher echocardiographic EF compared to baseline and other follow-ups (Repeat one-way ANOVA: F=4.4, p=0.024). Finally, nine of eleven patients had improved echocardiographic EF at the 36-month follow-up (Table 2). Subgroup analysis showed higher ECT-EF than baseline (MD: 4.8, p=0.017, n=8) in eight medium-high dosage cases (1*1010 and 2*1010 pfu) but not in three low dosage cases (5*109 pfu).

Compared to the control group, the experiment group showed a significant higher improvement of echocardiographic EF from baseline to 36-month follow-up (δEF: 3.5 ± 1.1 *vs.* -4.5 ± 1.3, MD: 8, p=0.0001). Subgroup analysis of the eight medium-high dosage cases suggested that experiment group had a trend of higher improvement of ECT-EF (baseline to 36-month follow-up) than control group (δEF: 4.8 ± 1.5 *vs.* 0.3 ± 1.7, MD: 4.5, p=0.08), although the difference did not reach the significant level.

Parameters	baseline	5-week	12-month	36-month
Safety parameters				
WBC (10^9/L)	6.8 ± 1.5	5.8 ± 1.2	7 ± 1.6	7.4 ± 1.6
Hb (g/L)	125.5 ± 12.9	127.3 ± 9.2	124.9 ± 10.6	125.9 ± 11.5
ALT (U/L)	25.6 ± 6.6	23.8 ± 4.2	25.9 ± 17.6	21.8 ± 11
AST (U/L)	22.3 ± 5.8	19.6 ± 2.6	22.3 ± 7.2	20.8 ± 7.5
BUN (mmol/L)	5.8 ± 1.2	3.9 ± 1.6	5.4 ± 1.9	5.3 ± 0.7
Cr (umol/L)	72.7 ± 30.9	73.2 ± 22.4	84.3 ± 29	69.2 ± 29.9
CEA (ng/mL)	1.3 ± 0.6	1.3 ± 0.8	1.7 ± 1.1	1.3 ± 1.2
AFP (ng/mL)	4.7 ± 2.4	4.4 ± 2.4	5.5 ± 3.2	3.9 ± 2.5
Efficacy parameters				
echocardiographic EF %	55 ± 8.9	55.6 ± 8.8	55.9 ± 8.4	58 ± 9.1*
ECT EF%	56.9 ± 15.5	59.7 ± 16.9	57.6 ± 13	59.2 ± 7

*P value<0.05 as compared with each other. WBC: White Blood Cell Count; Hb: hemoglobin; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BUN: Serum Urea Nitrogen; Cr: Creatinine; CEA: Carcino Embryonie Antigen; AFP: Alpha Fetoprotein; EF: Ejection Fraction; ECT: Emission Computed Tomography.

Table 2: Safety and efficacy parameters between baseline and follow-ups in the experiment group.

Discussion

Millions of patients are diagnosed with ischemic heart disease and ischemic heart failure. Over 80% of symptomatic coronary disease patients can be managed with conventional revascularization methods such as CABG or coronary stenting [13]. However more than 10% of patients with persisting symptoms and cannot be revascularized are referred to tertiary intervention centers [13]. These cases pose a therapeutic challenge which demands the exploration and evaluation of new methods of therapy.

Angiogenesis is a promising method for treating ischemic cardiac disease, which provides a new concept of revascularization [1]. HGF, one of the useful "angiogens", has shown potent angiogenic actions in ischemic tissues [1,14-16]. In our previous studies, we successfully inoculated ischemic animal models with high expressive Ad-HGF and achieved effective angiogenesis without apparent toxicity and mutation [6]. Our previous phase I clinical study demonstrated the short-term safety of intracoronary Ad-HGF administration for treating severe coronary disease in humans [9].

This study, a long-term follow-up of previous phase I clinical trial, confirmed the safety of intracoronary Ad-HGF administration for treating severe diffuse coronary disease. No death, no new-onset arrhythmia, no malignant tumor and no paroxysmal or long-term fever were recorded during the long-term follow-up. Although one stroke occurred, it did not seem to be directly related to the therapy.

Intracoronary Ad-HGF administration showed efficacy in improving echocardiographic EF during the 36-month follow-up, when compared not only to baseline but also with control group. Although ECT results did not reveal the significant improvement seen in echocardiographic EF, the medium-high dosage subgroup (1^*1010 and 2^*1010 pfu) also showed higher EF than baseline and higher δEF than control group. These results suggest that intracoronary Ad-HGF administration is efficient in improving EF of patients with severe diffuse coronary disease, and the efficacy may have a "dose-dependent" effect. It indicates that this new gene therapy might be a promising method to treat patients with diffuse coronary disease, who are not amenable to conventional revascularization or still have obvious symptoms after conventional revascularization of main coronaries.

This study has limitations in evaluating effectiveness of Ad-HGF. First, the number of alternative subjects is limited and the sample is small, so the difference between different dosages cannot be evaluated exactly. Second, due to the design, this study is just a controlled but not randomized trial, so the evidence level is not high. Next, our phase II clinical trial will be constructed to illustrate the effectiveness of Ad-HGF through another superior administration route (intramyocardial injection).

In conclusion, the results of the 3-year long-term follow-up of our previous phase I clinical trial, demonstrate that intracoronary Ad-HGF administration is safe and potentially efficient in improving EF of patients with severe diffuse coronary disease.

Funding

This study was supported by grants from "the Cardiovascular disease collaborative innovation center of Nanjing Medical University", "the Chinese Medical Association of the Sunlight Foundation (SCRFCMDA201217)", "the National Natural Science Foundation of China (No. 81170102/H0203)", "the Priority Acoronary diseaseemic Program Development of Jiangsu Higher Education Institutions (BL2012011)", "the Fourth Period Project "333" of Jiangsu Province (BRA2012207)", and "the Supporting program of Science and Technology of Jiangsu (Social Development, BK2010021)".

References

1. Aoki M, Morishita R, Taniyama Y, Kaneda Y, Ogihara T (2002) Therapeutic angiogenesis induced by hepatocyte growth factor: potential gene therapy for ischemic diseases. J Atheroscler Thromb 7: 71-76.
2. Jayasankar V, Woo YJ, Pirolli TJ, Bish LT, Berry MF, et al. (2005) Induction of angiogenesis and inhibition of apoptosis by hepatocyte growth factor effectively treats postischemic heart failure. J Card Surg 20: 93-101.
3. Azuma J, Taniyama Y, Takeya Y, Iekushi K, Aoki M, et al. (2006) Angiogenic and antifibrotic actions of hepatocyte growth factor improve cardiac dysfunction in porcine ischemic cardiomyopathy. Gene Ther 13: 1206-1213.
4. Li Y, Takemura G, Kosai K, Yuge K, Nagano S, et al. (2003) Postinfarction treatment with an adenoviral vector expressing hepatocyte growth factor relieves chronic left ventricular remodeling and dysfunction in mice. Circulation 107: 2499-2506.

5. Ahmet I, Sawa Y, Yamaguchi T, Matsuda H (2003) Gene transfer of hepatocyte growth factor improves angiogenesis and function of chronic ischemic myocardium in canine heart. Ann Thorac Surg 75: 1283-1287.
6. Wang W, Yang ZJ, Ma DC, Wang LS, Xu SL, et al. (2006) Induction of collateral artery growth and improvement of post-infarct heart function by hepatocyte growth factor gene transfer. Acta Pharmacol Sin 27: 555-560.
7. Aoki M, Morishita R, Taniyama Y, Kida I, Moriguchi A, et al. (2007)Angiogenesis induced by hepatocyte growth factor in non-infarcted myocardium and infarcted myocardium: up-regulation of essential transcription factor for angiogenesis, ets. Gene Ther 7: 417-427.
8. Taniyama Y, Morishita R, Aoki M, Nakagami H, Yamamoto K, et al. (2001) Therapeutic angiogenesis induced by human hepatocyte growth factor gene in rat and rabbit hindlimb ischemia models: preclinical study for treatment of peripheral arterial disease. Gene Ther 8: 181-189.
9. Yang ZJ, Zhang YR, Chen B, Zhang SL, Jia EN, et al. (2009) Phase I clinical trial on intracoronary administration of Ad-hHGF treating severe coronary artery disease. Mol Biol Rep 36: 1323-1329.
10. Yang ZJ, Xu SL, Chen B, Zhang SL, Zhang YL, et al. (2009) Hepatocyte growth factor plays a critical role in the regulation of cytokine production and induction of endothelial progenitor cell mobilization: a pilot gene therapy study in patients with coronary heart disease. Clin Exp Pharmacol Physiol 36: 790-796.
11. Yang ZJ, Wang E, Ma DC, Zhang Y, Wang L, et al. (2007) Recruitment of stem cells by hepatocyte growth factor via intracoronary gene transfection in the postinfarction heart failure. Sci China C Life Sci 50: 748-752.
12. Yang ZJ, Ma DC, Wang W, Xu SL, Zhang YQ, et al. (2006) Experimental study of bone marrow-derived mesenchymal stem cells combined with hepatocyte growth factor transplantation via noninfarct-relative artery in acute myocardial infarction. Gene Ther 13: 1564-1568.
13. Mukherjee D, Bhatt DL, Roe MT, Patel V, Ellis SG (1999) Direct myocardial revascularization and angiogenesis-how many patients might be eligible? Am J Cardiol 84: 598-600.
14. Morishita R, Aoki M, Hashiya N, Makino H, Yamasaki K, et al. (2004) Safety evaluation of clinical gene therapy using hepatocyte growth factor to treat peripheral arterial disease. Hypertension 44: 203-209.
15. Shimamura M, Sato N, Oshima K, Kurinami H, Waguri S, et al. (2004) Novel therapeutic strategy to treat brain ischemia: overexpression of hepatocyte growth factor gene reduced ischemic injury without cerebral edema in rat model. Circulation 109: 424-431.
16. Ishizawa K, Kubo H, Yamada M, Kobayashi S, Suzuki T, et al. (2004) Hepatocyte growth factor induces angiogenesis in injured lungs through mobilizing endothelial progenitor cells. Biochem Biophys Res Commun 324: 276-280.