SHORT COMMUNICATION

Chronic Myocarditis and Angiotensin-II Receptor Antagonist (TCV-116)

Kenichi WATANABE*1 Tohru IZUMI*2
Takafumi NAGATOMO*3 Takayuki INOMATA*1
Yasushi MIYAKITA*1 Masami SHIBA*1 Yukie OCHIAI*1
Fumiaki MASANI*2 and Akira SHIBATA*2

(Received on November 17, 1994)

*1 Division of Internal Cardiology, Tsubame Rosai Hospital
633 Sawatari, Tsubame City, Niigata 959-12, Japan
*2 First Department of Medicine, School of Medicine, Niigata University
*3 Department of Pharmacology, Niigata College of Pharmacy

A 46-year-old housekeeper with chronic myocarditis and congestive heart failure showed a dramatic response to a trial therapy employing the angiotensin-II receptor antagonist, TCV-116. On admission, her CPK was elevated and chest x-ray revealed huge cardiomegaly. The left ventricular (LV) chamber was markedly dilated, and the wall motion was reduced as assessed by echocardiography. On 99mTechnetium pyrophosphate (Tc-PYP) myocardial scintigraphy, intense positive staining projected to the lateral LV wall. When elevation of CPK recurred, the Tc-PYP uptake migrated to the other site, the postero-inferior wall. After trial-use of TCV-116, the patient's heart failure was improved and the Tc-PYP positive figure was eliminated completely. When the drug was withdrawn, Tc-PYP uptake reappeared. The new drug, TCV-116, seemed to be effective in the treatment of chronic myocarditis with congestive heart failure.

Key words: myocarditis, angiotensin-II receptor antagonist, TCV-116, myocardial necrosis, 99mTechnetium pyrophosphate myocardial scintigram

Introduction

In recent studies, myocardial necrosis has been shown to be suppressed by either angiotensin converting enzyme (ACE) inhibitors or angiotensin-II inhibitors, in cases caused by an elevated systemic and local angiotensin system in the heart(1~3).

The present patient suffered from chronic myocarditis with repetitive episodes of congestive heart failure. 99mTechnetium pyrophosphate (Tc-PYP) scintigraphy demonstrated a positive finding in the myocardium. In the
follow-up study, the active lesion seemed to migrate from the lateral cardiac wall to the other site despite the fundamental treatment. However, with the experimental use of a new angiotensin-II receptor antagonist, TCV-116 (Takeda Chemical Industries, Ltd.), given after informed patient consent and approval by the study committee, the positive uptake could be eliminated completely.

**Case Report**

The patient was a female, 46-year-old Japanese housekeeper. She had been an outpatient at our hospital, however due to the sudden occurrence of exertional dyspnea following a common cold, she was admitted. On admission, her chest x-ray demonstrated cardiomegaly with a cardio-thoracic ratio (CTR) of 0.72 and bilateral pleural effusion. Serum CPK and CPK-MB were elevated to 1426 (normal value=24~195) and 58 (normal value<6) IU/L, respectively. During her first admission, she received basic treatment for heart failure therapy (oral 40 mg furosemide and 0.125 mg digoxin) and CTR was decreased to 0.55. However after discharge she was hospitalized several times due to the repetitive occurrence of congestive heart failure. Every heart failure was associated with a mild episode of CPK-MB elevation. Two weeks prior to the last admission, the attacks of paroxysmal nocturnal dyspnea occurred again and she was hospitalized for the 6th time.

On admission, her CPK and CPK-MB were elevated to 1024 and 42 IU/L, respectively. The chest x-ray revealed severe cardiomegaly (CTR=0.65). A dilated left ventricular (LV) chamber (68 mm) was noted on two-dimensional echocardiography and hypokinesis was found in all segments of the heart (Fig. 1A). The electrocardiograms demonstrated a heart rate of 75 beats/min, sinus rhythm, and ST depression and T wave inversion in leads III, aVF and V5-6. With Tc-PYP, a positive staining was obtained at the lateral left ventricular wall (Fig. 1A). After the emergency care, she was treated with basic therapy for heart failure: oral 80 mg furosemide and 0.25 mg digoxin. Despite use of these drugs, elevation of CPK-MB reappeared again. Interestingly, at that time, the Tc-PYP active lesion migrated from the left lateral wall to the postero-inferior site (Fig. 1B). The ²⁰¹Thallium myocardial scintigram showed a partial defect at rest in the pyrophosphate positive region. At cardiac catheterization, LV pressures (systolic/diastolic/end-diastolic) were 102/3/9 mmHg. The cardiac index was 2.92 L/min/m². LV angiography showed very poor LV contraction; the ejection fraction (EF) was 26% (Fig. 2, left). The LV volumes were markedly increased (126 ml/m² was the end-diastolic volume index). Coronary arteries were normal (Fig. 2, left). Endomyocardial biopsies were sampled from the Tc-PYP scintigraphic positive LV wall (Fig. 2, right). They revealed only hypertrophied myofibers, but neither myocyte necrosis nor inflammatory cell infiltrates close to the damaged cardiocytes were noted. Antibody titers against enteroviruses were not elevated. The other laboratory data were follows: anti-nuclear antibody (−), anti-DNA antibody (−), ACE 10.3 IU/L, T₃ 1.01 ng/ml, T₄ 9.5 μg/dl, TSH 0.91 μIU/ml. There were no abnormalities in the cerebro-spinal fluid, in the mitochondria DNA of peripheral white blood cells, in the biopsies of the right quadriceps muscle and in the electromyogram. According to the above-mentioned data, we finally made a clinical diagnosis of chronic myocarditis, though positive biopsy findings of cell infiltrates were defective.
Because of the repetitive occurrence of congestive heart failure, she was given an angiotensin-II receptor antagonist (TCV-116) for 9 weeks (0.5 mg/day for 2 weeks, 1 mg/day for 2 weeks and 2 mg/day for the last 5 weeks). The positive Tc-PYP myocardial scintigraphic figure was eliminated completely (Fig. 1C). Her LV wall motion was improved in linkage with the change (Fig. 1C). Abstinence of this antagonist provoked recurrence of positive Tc-PYP staining in the same region and also aggravated her congestive heart failure (Fig. 1D).

Discussion

The present patient developed congestive heart failure following a common cold. Even in the first consultation, ST-T change on ECG, elevation of serum CPK-MB, cardiomegaly on chest x-ray and LV dysfunction were indicated. Probably because of the repetitive occurrence of congestive heart failure and CPK-MB elevations associated with their episodes, the acute myocarditis might have been “smoldering” from the initial attack and transformed into the chronic type. Currently, “chronic myocarditis” has been discussed as a prevailing concept, but the clinical entity has remained undefined. This disease is characterized either by 1) gradual worsening of cardiac function in the course of the acute myocarditis, or 2) repetitive occur-

**Fig. 1** Single photon emission computed tomography on 99mTc-Technetium pyrophosphate (Tc-PYP) myocardial scintigram (top) and echocardiogram (bottom).

A : Tc-PYP image on day 10 of hospitalization. Intense uptake is observed in the lateral left ventricular wall (arrow). Dilated left ventricular chamber and diffuse left ventricular hypokinesia.

B : Tc-PYP image on day 40 of hospitalization. Intense uptake is detected beyond the left ventricular postero-inferior wall (arrow).

C : Tc-PYP image after 9-week administration of TCV-116. The uptake on myocardium was completely eliminated. Slight improvement of hypokinesia in the left posterior wall.

D : Tc-PYP image after abstinence of TCV-116. Uptake recurred in the lateral left ventricular wall (arrow). Recurrent aggravation of hypokinesia is noted in the same left posterior wall.
The ejection fraction is 26% and the end diastolic volume index is 126 ml/m². Coronary arteries are normal. There are hypertrophied myofibers and fibrosis, but neither myocyte necrosis nor inflammatory cell infiltrates. (bar=100 μm)

The occurrence of congestive heart failure in the patient with biopsy-proven myocarditis. It is a problem in the present case that active myocarditis was not proven on histological analysis. It is well known, however, even if inflammatory change is not documented in the cardiac biopsies, myocarditis cannot be excluded, due to a possible sampling error. Endomyocardial biopsy is still the standard to make a diagnosis of myocarditis. Unfortunately the diagnostic role is limited to the positive cases. No definite conclusion can be made from negative samples. Although active myocarditis can be detected within 2 weeks from the onset of this disease, this invasive procedure is not always possible in critically ill patients. Hence, a radio-nuclear approach may have advantages as a non-invasive diagnostic tool, that can be easily repeated.

As shown here, Tc-PYP myocardial scintigraphy indicated a localized necrotic area. In chronic myocarditis one expects myocytolysis to be marginal only and infiltrating cells have to be documented nevertheless. Although myocyte necrosis was demonstrated by Tc-PYP scan, we did not find myocytolysis in the
biopsy. The biopsy was probably not taken from the affected area due to an error in sampling. Although the myocyte loss is so large as one would expect from the Tc-PYP or $^{67}\text{Ga}$-gallium scan, such a fulminant active myocarditis (this case and some other cases) did not fall into cardiogenic shock. This case did not show ST elevation, Q waves on ECG; she did not drink alcohol nor was she a habitual drug abuser. This case (dilated cardiomyopathy with positive Tc-PYP scan) may be diagnosed as chronic active myocarditis.

The diseases accompanied by CPK-MB elevation, myocarditis and systemic skeletal muscle disorders such as muscular dystrophy, mitochondrial encephalomyopathy and myopathy associated with hyperthyroidism should be considered. In the present patient, myocardial infarction could be excluded by coronary angiography. Muscular dystrophy was not detectable in her family history or in the dystrophin staining of muscle biopsies. Although there were no abnormalities in the biopsies of the right quadriceps muscle and in the electromyogram, CPK-MB was 42 IU/L (i.e. 4% of the CPK value). This case may be combined with latent localized myositis in correspondence with myocarditis. Mitochondrial encephalomyopathy was denied by DNA diagnosis. Thyroid function tests were quite normal. The muscle biopsies and electromyography excluded systemic myositis.

Although the echocardiogram demonstrated in addition pericardial thickening, the patient did not have pericardial effusion nor a friction rub. We suggest that she did not suffer from perimyocarditis. Overall, she was clinically diagnosed as repeated active phase of chronic myocarditis, because her positive data could be well explained by only the presence of chronic inflammation of her heart.

To reach a conclusion, radionuclear imaging was helpful. We employed this technique to monitor her clinical course. The Tc-PYP imaging is a popular tool to make the diagnosis of acute myocardial infarction within 1 week after the onset. In the literature, it has been pointed out that myocarditis also demonstrates a positive finding in Tc-PYP myocardial scintigram\(^8\).\(^9\). Although the role of $^{67}\text{Ga}$-gallium scintigraphy has been more prominent in the literature, this technique was not available for this patient. The Tc-PYP scintigram gave a positive finding in the lateral LV wall at admission. When elevated CPK-MB level recurred, the intense uptake immigrated from the initial site to the LV postero-inferior wall. It is known that the Tc-PYP scintigraphic diffuse uptake at the initial phase of acute myocarditis evolves into intense staining in the subsequent stage\(^8\).\(^9\). To date, no experience has been accumulated concerning the migration of the intense scintigraphic staining during a follow-up study other than in the present patient.

There are reports that steroids or immunosuppressants are effective in patients with chronic active myocarditis\(^8\).\(^9\). The present patient had not received these drugs, because active myocarditis was not proven histologically. At present, many investigators hesitate to start such a strong therapy for patients without obvious immunological disorders.

Recently, ACE inhibitors have been introduced for the treatment of hypertension and congestive heart failure. There are patients with hypertension or congestive heart failure that poorly respond to ACE inhibitors. The faint response may come from the production of an isoform of angiotensin-II which is synthesized by an ACE-independent pathway. TCV-116 is a new prodrug, synthesized by esterification of a carboxyl moiety in the CV-
11974 molecule, which shows specific antagonistic activity to the angiotensin-II subtype AT1 receptor. Unlike enalapril, this drug inhibits pressor responses induced by angiotensin I, II and III. It also excludes the bradykinin-induced hypotension. In experimental heart failure models in dogs and rats, this drug exhibited amelioration of cardiac function by the alleviation of preload and afterload without a direct influence on cardiac contractility. Therefore, this drug is also effective in non-responders to ACE inhibitors.

Tanaka et al. reported that, when TCV-116 was administered to mice with viral encephalomyocarditis, cardiocyte necrosis, cell infiltration and calcification were significantly alleviated in comparison with the control animal. These are good reasons to assume a similar mode of action in the present case who demonstrated complete elimination of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.

The alternative hypothesis would be that coronary vasospasm was the cause of myocardial uptake on Tc-PYP scintigram and alleviation of cardiac function after receiving TCV-116. From the present experience, it may be suggested that, like ACE inhibitors, TCV-116 inhibits cardiac muscle necrosis induced by angiotensin-II in the tissue.