Effect of Direct Renin Inhibitor, Aliskiren, on Peripheral Blood Monocyte Subsets and Myocardial Salvage in Patients With Primary Acute Myocardial Infarction

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Background: It remains unclear whether angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) have fully delivered the expected reduction in cardiovascular diseases. We investigated the effects of adding the direct renin inhibitor (DRI), aliskiren, to an ACEI or an ARB on monocyte subsets and myocardial salvage in patients with primary acute myocardial infarction (AMI).

Methods and Results: Twenty-one consecutive patients were treated with an ACEI or an ARB (non-DRI group), and another 21 consecutive patients received aliskiren combined with an ACEI or an ARB (DRI group). Two monocyte subsets (CD14\(^+\)CD16\(^-\) and CD14\(^+\)CD16\(^+\)) were measured by flow cytometry. The extent of myocardial salvage 7 days after AMI was evaluated by cardiac magnetic resonance imaging. Both plasma renin activity and aldosterone levels were significantly lower in the DRI group than in the non-DRI group. Peak levels of CD14\(^+\)CD16\(^-\) monocyte number and ratio were also significantly lower in the DRI group. The extent of myocardial salvage was significantly higher in the DRI group than in the non-DRI group (44.8 [41.2–53.1] vs. 36.0 [28.5–42.6], P=0.001).

Conclusions: A DRI combined with an ACEI or an ARB can better improve the extent of myocardial salvage after AMI than an ACEI or an ARB alone in association with the decrease in circulating CD14\(^+\)CD16\(^-\) monocytes. (Circ J 2012; 76: 1461–1468)

Key Words: Acute myocardial infarction; Magnetic resonance imaging; Monocytes; Myocardial salvage; Renin inhibitor

Timely percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) reduces mortality.\(^1\) Although this is a major advance, the rate of admissions with heart failure and the mortality rate in the chronic period have increased.\(^2\) Augmentation of the intrinsic wound healing that occurs during the first 1–2 weeks after AMI is a prospective approach with the potential to prevent heart failure.\(^3,4\) Monocytes and mature macrophages play a prominent part in the response to AMI recovery.\(^5,6\) The balance between host defense and repair mechanisms versus the pro-inflammatory properties of the mononuclear phagocytes in the injured myocardium should be taken into consideration for therapeutic targeting of monocytes/macrophages.

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The differential expression of CD14 and CD16 has enabled human monocytes to be divided into 2 subsets: CD14\(^+\)CD16\(^-\) and CD14\(^+\)CD16\(^+\) cells.\(^8,9,10\) Recently, we reported that the peak levels of CD14\(^+\)CD16\(^-\) monocytes are associated with the extent of myocardial salvage after AMI.\(^11\) Although CD14\(^+\)CD16\(^-\) monocytes represent a possible therapeutic target after AMI, it remains unclear whether manipulation of this subset of monocytes could affect the extent of myocardial salvage. Interestingly, Swirski et al revealed that angiotensin II (AngII) promotes the migration of mouse splenic Ly-6C\(^hi\) monocytes, which correspond to human CD14\(^+\)CD16\(^-\) monocytes, into the circulation.\(^12\) It remains unclear, however, whether angiotensin-converting enzyme inhibitors (ACEIs) or AngII type 1 receptor blockers (ARBs) have fully delivered the expected reduction in the development of post-infarction heart failure. In fact, optimum suppression of the renin-angiotensin system (RAS) is difficult to achieve with ACEIs and ARBs because both compensate for the elevation in plasma renin activity (PRA).\(^13\) Given that the overall activity of the RAS is regulated by renin activity.
and that the effects of ACEIs and ARBs are potentially attenuated by increased renin activity, it stands to reason that a logical approach to achieving complete RAS activity is required. The direct renin inhibitor (DRI), aliskiren, is a potent and specific inhibitor of human renin that reduces synthesis of all subsequent components in the cascade. Based on these findings, we hypothesized that adding aliskiren to treatment with an ACEI or an ARB could be beneficial in modulating the number and ratio of the monocyte subsets, leading to a reduction in myocardial damage. To investigate this hypothesis, we examined whether aliskiren has an additive effect on monocyte subsets and myocardial salvage in patients with primary AMI receiving conventional therapy including ACEIs or ARBs.
Effect of Aliskiren on Myocardial Salvage

Methods

This study was conducted in compliance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Wakayama Medical University. We also obtained written informed consent from all the patients prior to coronary angiography.

Study Population

The study population included 60 consecutive AMI patients admitted to Wakayama Medical University Hospital. Patients who had a history of AMI (n=3), renal insufficiency with baseline serum creatinine >1.5 mg/dl (n=2), atrial fibrillation (n=2), cardiogenic shock or unstable hemodynamic status (n=8), or were admitted >12 h from AMI onset (n=3) were excluded. The remaining 42 primary AMI patients who underwent PCI successfully within 12 h from the onset of AMI and fulfilled the diagnostic criteria for AMI were enrolled in this study. AMI was diagnosed when patients (1) experienced chest pain with >30 min and was not relieved by sublingual nitroglycerin; (2) showed ST-segment elevation and/or abnormal Q-wave on ECG; and (3) showed elevated serum creatine kinase (CK) levels. Exclusion criteria were: (1) diagnosed with AMI >12 h from the onset of symptoms; (2) prior MI; (3) cardiogenic shock or unstable hemodynamic status; (4) history of renal insufficiency (serum creatinine >1.5 mg/dl); (5) hyperkalemia (serum potassium >5 mmol/L); (6) difficulty performing cardiac magnetic resonance (CMR) imaging (eg, atrial fibrillation, presence of an implanted device, claustrophobia); (7) evidence of malignant disease; or (8) unwillingness to participate. All patients received emergent coronary angiography on admission and revascularization was successful with PCI.

Study Protocol

Twenty-one consecutive patients were treated with an ACEI or ARB (non-DRI group) and the other 21 consecutive patients received aliskiren 150 mg/day in addition to an ACEI or an ARB (DRI group). After PCI, an ACEI or ARB was administered within 24 h to all patients. In the DRI group, aliskiren was additionally administered within 24 h and, if required, oral nitrates, calcium antagonists, β-blockers, or diuretics were used.

Table 2. Comparison of Each Complication and Side Effects in the 2 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Non-DRI group (n=21)</th>
<th>DRI group (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>126±19</td>
<td>114±14</td>
<td>0.031</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74±13</td>
<td>69±12</td>
<td>0.200</td>
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<td>Serum creatinine, mg/dl</td>
<td>0.76±0.21</td>
<td>0.81±0.15</td>
<td>0.109</td>
</tr>
<tr>
<td>eGFR, ml·min⁻¹·1.73m⁻²</td>
<td>77.8±26.4</td>
<td>67.9±9.5</td>
<td>0.077</td>
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<tr>
<td>Serum kalium, mmol/L</td>
<td>3.9±0.4</td>
<td>4.2±0.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>0.83±0.25</td>
<td>0.71±0.16</td>
<td>0.006</td>
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<tr>
<td>2 weeks</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SBP, mmHg</td>
<td>125±11</td>
<td>113±10</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>67±9</td>
<td>65±12</td>
<td>0.492</td>
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<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.78±0.19</td>
<td>0.82±0.19</td>
<td>0.074</td>
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<tr>
<td>eGFR, ml·min⁻¹·1.73m⁻²</td>
<td>74.3±20.8</td>
<td>69.1±13.1</td>
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<td>Serum kalium, mmol/L</td>
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<tr>
<td>Total bilirubin, mg/dl</td>
<td>0.74±0.16</td>
<td>0.67±0.16</td>
<td>0.092</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

DRI, direct renin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

Figure 2. (A) Plasma renin activity (PRA) and (B) plasma aldosterone levels 8 days after the onset of acute myocardial infarction in patients treated with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II type 1 receptor blocker (ARB) alone (non-DRI group) or with aliskiren (direct renin inhibitor: DRI) in addition to an ACEI or an ARB (DRI group). Data are presented as box and whisker plots with median and 25th–75th percentiles (boxes) and 10th–90th percentiles (whiskers).

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added to the treatment regimen. All patients also received aspirin.

Clinical Parameters
Evaluated clinical parameters were age, sex, and coronary risk factors, which included hypertension (blood pressure ≥140/90 mmHg and/or a history of taking antihypertensive medication), diabetes mellitus (fasting plasma glucose ≥126 mg/dl, casual plasma glucose ≥200 mg/dl, or a diabetic pattern in the 75-g oral glucose tolerance test), hyperlipidemia (serum total cholesterol levels ≥220 mg/dl), obesity (body mass index ≥25 kg/m²), current smoking, and a family history of AMI. Peak CK and peak CK myocardial band levels were selected for analysis as indicators of AMI severity.

Cytometric Analysis
For cytometric analysis, monoclonal antibodies against CD14 (fluorescein isothiocyanate [FITC]-conjugated, clone M5E2, BD Bioscience, San Jose, CA, USA) and CD16 (phycoerythrin [PE]-CyTM5-conjugated, clone 3G8, BD Bioscience) were used as described previously. Matched isotype controls (FITC-conjugated mouse IgG2a isotype control, Clone G155-178, and PE-CyTM5 Mouse IgG1x isotype control, Clone MOPC-21; BD Biosciences) were used as negative controls. A total of 100μl of blood was incubated with saturating amounts of antibodies for 15 min at room temperature in the dark. For erythrocyte lysis and leukocyte fixation, 1 ml of lysing solution was added (BD FACs Lyse, Lysing Solution; Becton Dickinson, Germany).

Cytometric analysis was performed in a flow cytometer

Figure 3. Effect of aliskiren on myocardial salvage after acute myocardial infarction (AMI). The extent of myocardial salvage 7 days after AMI was evaluated by cardiac magnetic resonance (CMR) imaging as the difference between the areas of myocardium at risk (T2-weighted hyperintense lesion) and myocardial necrosis (delayed gadolinium enhancement). (A) Representative CMR imaging from patients in the non-DRI (Left) and DRI groups (Right) are shown. (B) The extent of myocardial salvage in the DRI group was significantly higher than in the non-DRI group. Data are presented as box and whisker plots with median and 25th–75th percentiles (boxes) and 10th–90th percentiles (whiskers). DRI, direct renin inhibitor.
Effect of Aliskiren on Myocardial Salvage

(BD FACSarian™, Becton Dickinson) using BD FACSDiva Software Systems (Becton Dickinson). Monocytes were first gated in a forward scatter/sideward scatter dot plot, and then 2-color fluorescence was measured within the monocyte gate. CD14+CD16+ cells were defined as monocytes expressing CD14, but not CD16. CD14+CD16+ cells were defined as monocytes expressing CD16 and either high levels of CD14 (CD14\textsuperscript{bright}CD16+), or lower levels of CD14 (CD14\textsuperscript{dim}CD16+). Thus, CD14\textsuperscript{bright}CD16+ and CD14\textsuperscript{dim}CD16+ were not analyzed separately, as in previous studies.\textsuperscript{18} The flow rate was set to low to minimize coincident events. Total monocyte events were at least 30,000 events per sample.

**Blood Sampling and Analysis**

Peripheral blood samples were collected from all study subjects as soon as possible after the diagnosis of AMI (before PCI) and on days 2, 3, 4, 5, 8, and 14 days after the onset of AMI. Whole blood samples obtained from all subjects were used immediately for flow cytometry. Neurohumoral measurements, including PRA and plasma aldosterone level, were performed 8 days after AMI. At 2 weeks after admission, side effects from the medications, such as hyperkalemia or renal dysfunction, were evaluated (Figure 1).

**CMR Imaging Protocol**

CMR imaging studies were performed using a 1.5-T clinical scanner (Intera Achieva, Philips Medical Systems, Best, The Netherlands) 7 days after the onset of AMI, as previously described.\textsuperscript{19,20} Patients were continuously monitored during the examination using single-lead ECG, repeated blood pressure measurements, and pulse oximetry. With the patient supine, contiguous short-axis cine images covering the left ven-

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**Figure 4.** Peak peripheral blood monocyte subset levels in the 2 treatment groups. (A) Representative fluorescence-activated cell scanner analysis of 2 monocyte subsets (CD14+CD16− and CD14+CD16+) derived from the non-DRI (Left) and DRI (Right) groups. Peak number (B) and ratio (C) of CD14+CD16+ monocytes in the DRI group were significantly lower than in the non-DRI group. Data are presented as box and whisker plots with median and 25th–75th percentiles (boxes) and 10th–90th percentiles (whiskers). DRI, direct renin inhibitor.
tricle from the base to the apex were acquired using a standard steady-state free-precession sequence. We then applied a breath-hold short-TI inversion-recovery pulse sequence (repetition time: 2 R-R intervals; echo time: 90 ms; slice thickness: 8 mm; field of view: 35 μm; matrix: 256 × 512) in 3 short-axis slices (basal, mid-ventricular, and apical) using a body coil. Each slice was obtained during an end-expiratory breath-hold of 12–15 s, depending on the patient’s heart rate.

We then acquired late enhancement (LE) images in the slice location with the maximum extent of T2 signal abnormality 10–15 min after intravenous injection of 0.1 mmol/kg gadolinium-diethylenetriamine penta-acid (Magnevist, Schering, Berlin, Germany). We used a 3-dimensional inversion-recovery turbo-gradient echo sequence, and images were obtained during an end-expiratory breath-hold. We optimized the inversion time (200–300 ms) to null the normal myocardium. The slice positions for both T2-weighted and LE acquisitions matched those of the cine images. There were no complications related to the CMR procedure, and all patients tolerated the procedure well.

CMR Imaging Data Analysis

All analyses were performed by consensus by 2 blinded observers (T.T. and K.K.) on an off-line workstation (View Forum, Philips Medical Systems, Eindhoven, The Netherlands). The extent of the area at risk (T2-weighted hyperintense lesion) and the extent of myocardial necrosis (delayed gadolinium enhancement) were quantified on the same slice location with 3 short- and 3 sagittal-axis slices, respectively. Percent salvaged myocardium was obtained as follows: 100 × extent of salvaged myocardium/extent of the myocardial area at risk.

Statistical Analysis

All statistical analyses were performed using the statistical software package SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as mean ± standard deviation for approximately normally distributed variables and median (interquartile range) for skewed variables (according to the Shapiro-Wilks test). Categorical data are presented as numbers (%). Differences between groups were assessed using the unpaired t-test for approximately normally distributed variables, the Mann-Whitney test for skewed variables, and the chi-square test or Fisher’s exact test as appropriate for categorical variables. Comparison between on admission and 2 weeks later was performed with the paired t-test. Correlation between 2 parameters was analyzed by Spearman’s rank correlation test. Values of P < 0.05 were considered statistically significant.

Results

Patient Characteristics

The patient characteristics of both groups are summarized in Table 1. No statistically significant differences were found in terms of age, sex, coronary risk factors, or medications on admission, including antihypertensive agents (ACEIs or ARBs, β-blockers, calcium-channel blockers), between the 2 groups. The following individual RAS blockers were being received at admission in each group. Non-DRI group: enalapril 2.5 mg/day in 16 (76%), candesartan 8 mg/day in 3 (14%), and valsartan 80 mg/day in 2 (10%); DRI group: enalapril 2.5 mg/day in 17 (80%), 5 mg/day in 2 (10%), and candesartan 8 mg/day in 2 (10%). All patients received statin therapy within 24 h from the onset of AMI. Furthermore, intracoronary or intravenous administration of nicorandil was performed in 7 patients (33%) in the non-DRI group and 5 (24%) in the DRI group (P = 0.50). Patients in the non-DRI and DRI groups did not have any serious complications or side effects such as hyperkalemia or renal dysfunction (Table 2).

Effect of Aliskiren on PRA and Plasma Aldosterone

Both the PRA (Figure 2A) and plasma aldosterone levels (Figure 2B) in the DRI group were significantly lower than those in the non-DRI group (PRA: 0.2 [0.1–0.6] ng·mL⁻¹·h⁻¹ vs. 1.8 [0.7–7.6] ng·mL⁻¹·h⁻¹, P < 0.001; aldosterone: 38.1 [28.8–
Effect of Aliskiren on Myocardial Salvage

The extent of myocardial salvage in both groups is represented in Figure 3A. The extent of myocardial salvage in the DRI group was significantly higher than in the non-DRI group (44.8 [41.2–53.1] vs. 36.0 [28.5–42.6], P<0.001) (Figure 3B).

Effect of Aliskiren on Peripheral Blood Monocyte Subset Levels

Because we had previously shown that peak levels of CD14+/CD16− monocytes were negatively associated with the extent of myocardial salvage,11 we examined the effects of adding aliskiren to an ACEI or an ARB on monocyte subsets following AMI. Representative fluorescence-activated cell scanner analyses in 2 monocyte subsets derived from the non-DRI and DRI groups are shown in Figure 4A. The peak number (Figure 4B) and ratio (Figure 4C) of CD14+/CD16− monocytes in the DRI group were significantly lower than in the non-DRI group. As expected, the peak number (Figure 5A) and ratio (Figure 5B) of CD14+/CD16− monocytes negatively correlated with the extent of myocardial salvage in both the non-DRI and DRI groups.

Discussion

In this study we demonstrated for the first time that adding aliskiren to ACEI or ARB therapy improved myocardial salvage after AMI. Although the detailed mechanisms in terms of the favorable effects of aliskiren on post-infarction myocardial recovery remain unclear, inhibition of excessive CD14+/CD16− monocyte recruitment, possibly through dual inhibition of the RAS, may be important. The biological properties of monocyte subsets and their sequential recruitment to the infarct area correlate with the time course of tissue healing. The early inflammatory and digestive phase 1 is followed by active resolution of inflammation and tissue repair in phase 2. A well-coordinated biphasic monocyte response is necessary for proper healing. Abrogation of phase 1 impairs the removal of dead cardiac myocytes and debris, whereas abrogation of phase 2 decreases the generation of microvessels and deposition of collagen. In our previous study, patients with AMI showed a similar biphasic monocyte response. A longitudinal study of a cohort of 36 patients over the course of 2 weeks after AMI demonstrated that circulating inflammatory CD14+/CD16− monocytes expanded first (peak on day 2.6), followed by CD14+/CD16+ monocytes (peak on day 4.8). These findings are in line with studies in mice, which showed that the equivalent Ly-6C<sup>high</sup> and Ly-6C<sup>low</sup> monocytes peak at similar times post-infarction (on days 3 and 5–7, respectively). The paradigm shift from a monophasic to biphasic monocyte response after AMI offers new therapeutic strategies. For instance, it may be beneficial to modulate the number and ratio of the subsets of monocytes to enhance tissue repair or prevent tissue damage. Swirski et al have shown that AngII promotes migration of splenic Ly-6C<sup>high</sup> monocytes into the circulation. They have also shown that an increase in the circulating concentration of AngII after MI induces the dimerization of the AngII type 1 receptor on Ly-6C<sup>high</sup> monocytes, boosting the level of these monocytes. Although ACEIs and ARBs both offer robust reductions in cardiovascular mortality in patients after AMI, much clinical evidence shows that higher doses of these RAS blockers fail to achieve more beneficial clinical outcomes for AMI patients. Despite the success of high-dose ACEI- or ARB-based therapies to achieve more inhibition of tissue or circulating AngII levels, these agents promote a reflex rise in PRA. Although the predictive value of PRA remains debatable, it was shown to predict MI in stroke survivors enrolled in the Perindopril Protection Against Recurrence Stroke Study. In the present study we showed that the peak levels of CD14+/CD16− monocytes were significantly lower in the DRI group than in the non-DRI group. This study also showed that PRA in patients with the combination therapy of an ACEI/ARB plus aliskiren was significantly lower than in patients treated with an ACEI/ARB alone. Importantly, the present study demonstrated for the first time that adding aliskiren to an ACEI or ARB therapy improves myocardial salvage. Taken together, the direct inhibitory effect of PRA by aliskiren may be independently associated with greater reduction in the number of CD14+/CD16− monocytes and improved myocardial salvage. These results are in line with previous clinical studies, which include the beyond blood pressure-mediated renal benefits noted in patients with diabetic nephropathy (Aliskiren in the Evaluation of Proteinuria in Diabetes [AVOID] Trial) and profound reductions in blood natriuretic peptide noted in ACEI-/ARB-treated patients with heart failure.

Study Limitations

First, the results are prospective in terms of patient enrollment, but observational in nature. Thus, our study does not provide a mechanistic explanation for the improvement in myocardial salvage in patients treated with the DRI aliskiren combined with an ACEI or an ARB. Second, we cannot determine whether the increase in the peak levels of CD14+/CD16− monocyte numbers and ratio reflects the extent of monocyte infiltration into ischemic myocardium. Third, although we found that both the CD14+/CD16− monocyte numbers and ratio negatively correlated with the extent of myocardial salvage, we cannot determine which is more important. However, through extrapolation of experimental and clinical data, Nahrendorf et al recently proposed the hypothetical parabolic relationships of inflammatory monocyte numbers and the healing outcome. That is, insufficient as well as exaggerated monocyte numbers are associated with impaired healing. Although the hypothesis suggests that the absolute number of monocytes is more important in intervening for the salvage of myocardium, further studies are needed on this clinically important issue. Finally, although we performed a CMR imaging assessment of myocardial salvage 7 days after reperfusion, we cannot exclude the possibility that earlier assessment would have influenced the extent of myocardial salvage.

Clinical Implications

AMI is the most common cause of heart failure. The combination of reduced acute infarct mortality by successful and prompt restoration of blood flow by PCI and then insufficient options for the chronic treatment of infarct survivors has contributed to an increased prevalence of heart failure. It remains unclear whether current standard therapy with β-blockers, and ACEIs or ARBs has fully delivered the expected reduction in cardiovascular diseases. Therefore, it is crucial to explore new therapeutic strategies to repair the failing heart after AMI. This study has shown for the first time that adding aliskiren to ACEI or ARB therapy improves myocardial salvage, which is accompanied by lower blood levels of CD14+/CD16− monocytes. The nature of the inflammatory response during infarct healing should be further investigated because it may provide a key to pharmacological treatment options for patients with AMI.
Conclusions

Aliskiren in addition to an ACEI or an ARB improved the extent of myocardial salvage in patients with AMI who underwent successful PCI. These favorable effects of aliskiren might be related to suppression of not only the RAS cascade but also excessive recruitment of CD14+CD16− monocytes. Although further studies are needed to understand the role of monocytes in post-MI recovery/injury, aliskiren could become an alternative therapy for salvaging ischemic, damaged myocardium.

Acknowledgment

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References


