**Background:** The therapeutic strategy for giant cell myocarditis (GCM) remains controversial, so we reviewed the clinical status of Japanese patients with GCM.

**Methods and Results:** We retrospectively reviewed 6 consecutive patients with GCM requiring percutaneous mechanical circulatory support (p-MCS), with 3 further requiring ventricular assist devices. One patient died during p-MCS. Cardiac function improved in the other 5 with immunosuppressive therapy, but only 3 patients treated with dual immunosuppressants, including cyclosporine (CyA), achieved >1-year survival.

**Conclusions:** The prognosis of patients with fulminant GCM is poor, but a treatment that combines MCS and early administration of CyA-based immunosuppressants will be useful.

**Key Words:** Giant cell myocarditis; Immunosuppressants; Mechanical circulatory support
course, and outcomes, were retrospectively assessed through a review of patients’ medical records.

Statement on Ethics
Our case series study was exempted from the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” established by the Japanese government. As per the institutional ethics guidelines, however, informed consent for publication was obtained from the patients or their next of kin.

MCS Strategies for Patients With GCM
All patients initially received temporary p-MCS, such as intra-aortic balloon pumping (IABP) and/or percutaneous extracorporeal membrane oxygenation (p-ECMO), as a life-saving intervention. If the systemic condition was not stabilized after short-term support, a pVAD was implanted. The Nipro-Toyo VAD (Nipro-VAD, Nipro, Osaka, Japan) was used for LV support and ECMO followed by implantation of the Nipro-Toyo VAD for right ventricular support.

Results
Baseline Clinical Characteristics and Presentation
Patients 2, 4, and 5 had concurrent autoimmune diseases, comprising myasthenia gravis, hyperthyroidism and polyarthritis with alopecia. All patients were screened for antinuclear antibodies, with patient 4 testing positive for anticentromere antibody (+).

Table 1. Characteristics of the Study Patients

| Patient no. | Sex | Age (years) | Underlying disease | p-MCS | VAD | Time from the initial symptoms to primary MCS (days) | p-MCS period (days) | VAD support period (days) | Complications | Outcome | Follow-up period after MCS weaning (days) |
|-------------|-----|-------------|-------------------|-------|-----|---------------------------------|-------------------|-------------------------|--------------|---------|------------------------------------------|
| 1           | M   | 57          | None              | IABP  | p-ECMO | –                               | 10                | 18                      | Stroke, pneumothorax   | Died on p-ECMO | NA                                      |
| 2           | F   | 58          | Myasthenia gravis | IABP  | p-ECMO | LVAD                            | 61                | 6                       | Mediastinitis, SAH, pneumothorax, cholecystitis, CRBSI | Died after MCS removal Recurrence (–) | 65                      |
| 3           | M   | 61          | None              | IABP  | p-ECMO | BVAD                            | 9                 | 12                      | Sepsis, GIB, ARF, DVT | Died after MCS removal Recurrence (–) | 43                      |
| 4           | F   | 50          | Hyperthyroidism, anticentromere antibody (+) | IABP  | – | 8                               | 8                 | 8                       | Steroid myopathy       | Alive after MCS removal Recurrence (–) | 1,142             |
| 5           | M   | 62          | Polyarthritis, alopecia | IABP  | LVAD | 24                               | 8                 | 71                      | Prostatitis, septic shock due to CRBSI | Died after MCS removal Recurrence (+) | 683                      |
| 6           | F   | 77          | Pituitary adenoma | IABP  | p-ECMO | –                               | 395               | 9                       | PAF, NSVT, GIB, steroid diabetes | Alive after MCS removal Recurrence (–) | 452                      |

ARF, acute renal failure; BVAD, biventricular assist device; CRBSI, catheter-related blood stream infection; DVT, deep venous thrombosis; GIB, gastrointestinal bleeding; IABP, intra-aortic balloon pumping; LVAD, left ventricular assist device; NSVT, non-sustained ventricular tachycardia; PAF, paroxysmal atrial fibrillation; p-ECMO, percutaneous extracorporeal membrane oxygenation; p-MCS, percutaneous mechanical circulatory support; SAH, subarachnoid hemorrhage; VAD, ventricular assist device.

However, patients 1, 2, 3, and 5 presented with impaired cardiac conduction, requiring temporary or permanent pacemaker implantation, without a defibrillator. Echocardiography was completed in all 6 patients before p-MCS. The median LV end-diastolic dimension (LVDd) was 54.5 mm (range, 40–56 mm), with a median LV ejection fraction (LVEF) of 14% (range, 10–39%).

Treatment Course and Immunosuppression
All 6 patients experienced cardiogenic shock and received temporary p-MCS at a median of 17 days after the onset of symptoms. Patients 2, 3, and 5 ultimately required a pVAD. Of note, no patient was further treated with an implantable LV assist device (LVAD) or HTx. Patient 3 required biventricular support, with the right VAD established at the time of LVAD (Table 1).

With regard to immunosuppressive therapy, only patient 6 was treated with steroids and CyA, with a target trough level of 100–150 ng/mL, prior to MCS. However, during MCS, all patients received steroid therapy. With the exception of patient 2, patients were first treated with high-dose corticosteroid pulse therapy, followed by oral steroid therapy. Patients 4, 5, and 6 were additionally started on oral CyA, with a target trough level of 100–150 ng/mL, while on MCS, with this dual immunosuppressive therapy maintained after MCS removal (Table 2).

Patients 4 and 6 continue to be managed with low-dose steroid and CyA therapy via the outpatient clinic, with a target trough level of 50 ng/mL and 100 ng/mL, respectively. Patient 4 used 5 mg of prednisolone (PSL) as a maintenance dose, discontinuing PSL at 2 years after GCM onset.

Patients 1, 2, 3, and 5 received intravenous immunoglobulin treatment; of note, none of these patients were treated using muromonab-CD3 or anti-thymocyte globulin. Patients 2, 4, 5, and 6 were treated using angiotensin-
serum levels of troponin T (Figure D), and the patients were weaned from MCS, after a median period of 22 days (range, 8–78 days). Recurrence of GCM was identified in patient 5, early after LVAD removal, but without new injury to the myocytes detected. The patient was successfully treated using high-dose corticosteroid pulse therapy. Ultimately, for all 3 patients (2, 3, and 5) treated using VAD, although hemodynamics were stable for a while, cardiac function gradually deteriorated after VAD removal and all 3 patients died of multiple organ failure due to low converting enzyme inhibitors after their systemic condition stabilized, with patients 4 and 6 further treated using β-blockers.

Outcomes and Adverse Events
Patient 1 did not recover cardiac function and died from multiple organ failure while on p-ECMO support, on day 18 after initiation of p-MCS treatment (Table 1). After immunosuppressive therapy, cardiac function improved in the remaining 5 patients (Figure A–C), with a decrease in serum levels of troponin T (Figure D), and the patients were weaned from MCS, after a median period of 22 days (range, 8–78 days). Recurrence of GCM was identified in patient 5, early after LVAD removal, but without new injury to the myocytes detected. The patient was successfully treated using high-dose corticosteroid pulse therapy. Ultimately, for all 3 patients (2, 3, and 5) treated using VAD, although hemodynamics were stable for a while, cardiac function gradually deteriorated after VAD removal and all 3 patients died of multiple organ failure due to low

| Number | Time from initial symptoms to immunosuppression (days) | Before p-MCS | While on p-MCS | While on VAD | After MCS weaning |
|--------|--------------------------------------------------------|--------------|----------------|--------------|------------------|
| 1      | 15                                                     | None         | mPSL → hydrocortisone | –            | –                |
| 2      | 66                                                     | None         | mPSL            | None         | mPSL (secondary pulse therapy for eosinophil infiltrate) |
| 3      | 23                                                     | None         | None            | mPSL → PSL   | PSL              |
| 4      | 8                                                      | None         | mPSL → PSL+CyA  | –            | PSL+CyA          |
| 5      | 31                                                     | None         | None            | mPSL → PSL+CyA | mPSL (secondary pulse therapy for GCM recurrence) → PSL+CyA |
| 6      | 394                                                    | mPSL → PSL+CyA | mPSL → PSL+CyA | –            | PSL+CyA          |

CyA, oral cyclosporine; GCM, giant cell myocarditis; p-MCS, percutaneous mechanical circulatory support; mPSL, methylprednisolone pulse treatment; PSL, oral prednisolone; VAD, ventricular assist device.

Figure. Changes in the clinical parameters during hospitalization in 6 patients with giant cell myocarditis. Echocardiography data for (A) left ventricular ejection fraction (LVEF) and (B) LV end-diastolic dimension (LVDd). Serum levels of (C) B-type natriuretic peptide (BNP) and (D) troponin T. The solid lines indicate the change in the parameters in patients 4 and 6, the dotted lines for patient 1, and the dashed lines for patients 2, 3 and 5 who received a ventricular assist device.
output syndrome or subsequent sepsis. The autopsy results of patient 3 showed severe myocardial replacement fibrosis with lymphocytic infiltration, without apparent infiltration of giant cells.

Patients 4 and 6 did not require VAD or re-implantation of MCS and were discharged home. They survived for >1 year after p-MCS discontinuation, with preservation of cardiac function (LVEF of 54% and 58%, respectively, and LVDd of 48 mm and 47 mm, respectively).

With regard to adverse events, an infection developed during device support in 2 of the 6 patients: patient 2 developed mediastinitis and patient 5 developed septic shock caused by a catheter-related bloodstream infection. There were no incidents of device-related infection.

Discussion

We reviewed the clinical and disease outcomes for 6 patients with fulminant GCM, and report poor outcomes for patients requiring pVAD treatment. Previous research has reported an extremely poor prognosis for patients with GCM, with a mean survival period of 3 months when immunosuppressive therapy is not used.1 In recent years, immunosuppressants, and CyA principally, have been widely used as a component of the treatment of GCM, with evidence of improvement in the HTx-free survival rate.3,4 However, evidence of outcomes in patients with GCM requiring MCS support is limited to small case series studies, with the immunosuppressant regimen used in those cases not having been fully clarified. Although treatment of GCM without immunosuppressive therapy or a single immunosuppressant course of steroids has often been accepted, the HTx-free survival in these cases is very low.5,6,8–10 Of note, a few studies have reported favorable outcomes in patients with fulminant GCM requiring MCS support when treated early with an aggressive immunosuppressant protocol.4,10 In our case series, single steroid immunosuppressive therapy was used in patients 1, 2, and 3 to prevent device-related infection; however, the clinical course of these patients was not favorable. Based on these outcomes, we currently use a standard immunosuppressant regimen of a combination of steroid and CyA for the treatment of GCM, even under MCS support. Specifically, our combined regimen consists first of high-dose corticosteroid pulse therapy, followed by oral steroid (≈1 mg PSL per kg body weight) and CyA therapy with a target trough level of 100–150 ng/mL, with the dose of oral steroid reduced over time, at a rate of 5 mg PSL per week. We regularly monitor the serum level of troponin T during the decreasing phase of oral steroids, with an increase in troponin T level indicative of a suspected relapse of GCM. Note that we routinely perform an endomyocardial biopsy during the steroid reduction phase, regardless of any change in the serum level troponin T level. Over the longer term, the dose of CyA is reduced to a target trough of 60–70 ng/mL, equivalent to the level used for chronic maintenance of immunosuppressive therapy after HTx; however, further experience is needed to fully clarify the appropriate dosage and duration of immunosuppressive therapy.

The successful use of p-MCS and/or VAD for the treatment of patients with fulminant lymphocytic myocarditis, and HTx as required, has previously been reported, with no disease recurrence.11 However, MCS therapy for GCM is challenging in situations where we can use MCS support only as a bridge-to-recovery intervention. Unlike patients with typical fulminant lymphocytic myocarditis, the patients with GCM in our case series did not present with a marked elevation in CK-MB levels, and 5 of the 6 patients achieved temporary improvement in cardiac function after immunosuppressive therapy, with successful weaning from MCS support. However, the 3 patients who required additional VAD support showed poor disease prognosis, with all 3 developing circulatory failure after cessation of LVAD and dying of multiple organ failure, without evidence of GCM recurrence. The main reason for VAD removal was to avoid VAD-related complications, as well as long-term immunosuppressive therapy under VAD support. The decision for early VAD removal was motivated, in part, by the difficulty in establishing HTx candidacy and the non-availability of destination therapy (DT) in Japan. By comparison, the 2 patients who did not require LVAD support achieved an excellent LVEF recovery of >50%, with a good overall clinical course. These patients received a combination of steroid and CyA therapy, either before or during p-MCS. We do note that, although baseline LV function was not necessarily different in these patients, compared with the other patients with a worse clinical outcome, these patients did not experience a conduction disorder. The absence of infectious complications may also have contributed to the favorable outcomes in these patients. We propose that an attempt should be made to achieve recovery of cardiac function, without transitioning to advanced therapeutic stages, such as use of VAD, by introducing sufficient immunosuppressive therapy before or during p-MCS. This would be particularly important in the current situation where there is little-to-no option to move to the treatment phase of HTx.

According to the 2017 data from the United Network for Organ Sharing Registry, the 10-year survival rate after HTx for patients with GCM is 68%, which is not different to the rate for any other disease requiring HTx.12 Although 6–25% of all patients with GCM experience disease relapse after HTx, the response of these patients to immunosuppressive therapy is generally good.1,3,4 In our case series, patients who were weaned off LVAD despite incomplete recovery of cardiac function had a poor prognosis. With future approvals of DT, it may be possible that patients with GCM might be able to receive long-term circulatory support using an implantable LVAD to further improve their long-term prognosis. Even in such cases, immunosuppressive therapy should be continued to maintain cardiac function, especially the function of the right heart on VAD support.

In our case series, there was no incidence of device-related infection after the initiation of immunosuppressive therapy, although some patients did develop systemic infections. This may be because in all patients, the device support period did not extend beyond 78 days, regardless of the type of mechanical system used to support cardiac function. It is possible that device-related infection might pose a problem if a long-term implantable LVAD is used, which will need to be considered. Biopsy-guided adjustment of the intensity of immunosuppressive therapy can lower the risk of device-related infection, as well as other opportunistic infections. It is possible that, in the future, indications for HTx in patients with GCM could be re-evaluated after confirming patient prognosis after long-term LVAD support using DT.
The limitations of our case series need to be acknowledged. First, the number of patients with GCM in Japan is relatively low compared with Western countries, even if our institution is one of the high-volume centers for heart failure treatment in Japan. Therefore, we cannot conclude that a particular treatment strategy is correct from our case series; more precise investigations, using data from multicenter databases, are warranted to clarify the most effective treatment approach for GCM. Second, due to the mandate of our institution, less severe cases of GCM are not referred to our institution and, as such, the patients evaluated in our study may not accurately represent the range of characteristics of patients with GCM.

Conclusions
The rate of MCS use in patients with GCM is high, and patient prognosis is poor. In particular, patients who ultimately require VAD often do not achieve long-term survival in Japan, where HTx candidacy for GCM cannot be easily obtained and DT has not been approved. A therapeutic strategy that combines MCS and early administration of CyA-based multiple immunosuppressive therapies will be useful.

Disclosures
The authors declare that they have no conflicts of interest.

References
1. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis: Natural history and treatment. Multicenter giant cell myocarditis study group investigators. N Engl J Med 1997; 336: 1860–1866.
2. Kodama M, Matsumoto Y, Fujiwara M, Masani F, Izumi T, Shibata A. A novel experimental model of giant cell myocarditis induced in rats by immunization with cardiac myosin fraction. Clin Immunol Immunopathol 1990; 57: 250–262.
3. Kandolin R, Lehtonen J, Salmenkivi K, Räisänen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ Heart Fail 2013; 6: 15–22.
4. Ekström K, Lehtonen J, Kandolin R, Räisänen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. Eur J Heart Fail 2016; 18: 1452–1458.
5. Murray LK, Gonzalez-Costello J, Jonas SN, Sims DB, Morrison KA, Colombo PC, et al. Ventricular assist device support as a bridge to heart transplantation in patients with giant cell myocarditis. Eur J Heart Fail 2012; 14: 312–318.
6. Suarez-Barrientos A, Wong J, Bell A, Lyster H, Karagiannis G, Banner NR. Usefulness of rabbit anti-thymocyte globulin in patients with giant cell myocarditis. Am J Cardiol 2015; 116: 447–451.
7. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, et al. Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol 2008; 102: 1535–1539.
8. Brilakis ES, Olson LJ, Berry GJ, Daly RC, Loizance D, Zucker M, et al. Survival outcomes of patients with giant cell myocarditis bridged by ventricular assist devices. ASAIO J 2000; 46: 569–572.
9. Montero S, Aissouai N, Tadié JM, Bizouarn P, Scherrer V, Persichini R, et al. Fulminant giant-cell myocarditis on mechanical circulatory support: Management and outcomes of a French multicentre cohort. Int J Cardiol 2018; 253: 105–112.
10. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, et al. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. Circulation 2017; 136: 529–545.
11. Asaumi Y, Yasuda S, Morii I, Kakuchi H, Otsuka Y, Kawamura A, et al. Favorable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. Eur Heart J 2005; 26: 2185–2192.
12. Elamm CA, Al-Kindi SG, Bianco CM, Dhakal BP, Oliveira GH. Heart transplantation in giant cell myocarditis: Analysis of the United Network for Organ Sharing Registry. J Card Fail 2017; 23: 566–569.