It is well established that long-term administration of angiotensin-converting enzyme (ACE) inhibitors has a favorable effect in patients with chronic heart failure and dilated cardiomyopathy. However, less information is available on patients whose left ventricular ejection fraction normalizes after an episode of systolic dysfunction secondary to acute myocarditis. We followed 35 patients who were diagnosed at our center between 1987 and 1995 with acute myocarditis and an ejection fraction <45%. All were taking ACE inhibitors. After 34 (23) months of follow-up, the left ventricular ejection fraction was >50% in all 35 patients. Treatment with ACE inhibitors was discontinued in 15 of the 35 patients, while the other 20 continued ACE inhibitor therapy. After 3 years of follow-up, no death had occurred, but the incidence of new episodes of heart failure with a left ventricular ejection fraction <45% was higher in patients who stopped taking ACE inhibitors (33% vs 5%, \(P=.064\)), and their ejection fraction was lower (47 \[12\%\] vs 57 \[11\%\], \(P=.002\)). These results suggest that ACE inhibitors should be continued over the long term in these patients.

Key words: Acute myocarditis. ACE-inhibitors. Prognosis.

INTRODUCTION

Numerous studies have been performed on the long-term prognosis of patients with chronic heart failure due to left ventricular systolic dysfunction (dilated cardiomyopathy) of different etiology, and much evidence has been collected on the benefits of drugs such as angiotensin converting enzyme inhibitors (ACE inhibitors) and beta-blockers with respect to this prognosis.\(^1\) However, the natural history of patients with systolic dysfunction and recently developed heart failure due to acute myocarditis is less well known. Neither is it known...
whether treatment with ACE inhibitors should be
maintained over the long term in patients whose left
ventricular ejection fraction (LVEF) normalizes after the
period of dysfunction. To investigate this, the data for 35
consecutive patients diagnosed at our center between
1987 and 1995 with severe left ventricular systolic
dysfunction due to acute myocarditis, and in whom the
LVEF normalized after treatment, were reviewed.

METHODS

The characteristics of the patients, the inclusion criteria,
the study protocol, and the results after five years of
follow-up have been published elsewhere.2 Clinical,
echocardiographic and radioactive isotope criteria were
used to arrive at a diagnosis of acute myocarditis, ie,
recently developed heart failure (less than two weeks),
an LVEF of <45%, a non-dilated left ventricle (end-
diastolic diameter normal for patient age and body surface
area), diffuse distribution of necrosis markers in the
myocardium (anti-myosin antibodies labeled with indium-
111), and the exclusion (via echocardiography, myocardial
perfusion gammagramy, and coronary angiography) of
any other cause of left ventricular dysfunction. The LVEF
was determined by echocardiography (initial LVEF 27
[8%]) using the Simpson method. All patients initially
received ACE inhibitors, diuretics and digoxin.

At 34 (23) months the LVEF had normalized in all 35
patients (mean LVEF 57 [11%]); all continued to receive
ACE inhibitors. None of the patients received diuretics
at this time, and only those with atrial fibrillation (five
patients, 16%) were administered digoxin. At this point
the patients were released from attending further
appointments at our center, although they were still
followed by their normal cardiologists who were at liberty
to decide on their continued use of ACE inhibitors. Five
years later the patients again attended an appointment at
our center, and a comparison was made between those
who had continued with ACE inhibitors and those who
had not. The #X2 or Fisher's exact test was used to
compare qualitative variables; the Student t test was used
to compare quantitative variables.

RESULTS

All 35 patients released to normal care had an LVEF
>50%. The habitual cardiologists of 15 patients (42%)
decided to suspend the use of ACE inhibitors; the
remaining 20 patients (58%) continued to take them. The
demographic and clinical characteristics of both groups
of patients were similar (Table), as was the treatment
they received (with the exception of ACE inhibitors).
The LVEF in both eventual groups of patients was similar
at the time of release from our center (56 [8%] and 57
[8%]), all were asymptomatic, and the prevalence of atrial
fibrillation in both was similar (13% and 15%) (Table).
At that moment of release no patient was being treated
with diuretics or beta-blockers; digoxin was used for the
control of atrial fibrillation in two patients who would
eventually no longer receive ACE inhibitors (13%) and
in three patients who would continue to receive them
(15%).

No patient died during follow-up. However, the
incidence of new episodes of heart failure with
LVEF<45% was higher in the group that stopped using
ACE inhibitors (33% compared to 5%; P=.064). In all
cases this heart failure was moderate (four patents fell
into NYHA functional class functional II and two into
class III). None of these patient needed to be readmitted
to hospital and all improved with diuretics and ACE
inhibitors. These six patients were also administered
beta-blockers. The mean LVEF during the
decompensation period in these patients was 37 (7%),
but was seen to have increased to 52 (8%) during
echocardiographic tests performed six months later. In
only one of these six patients - a patient who had stopped
taking ACE inhibitors - did the LVEF fail to normalize
after the reintroduction of these drugs and beta-blockers;
at the 5 year follow-up examination it was still at 35%.
No important differences were seen between the
characteristics of these six patients and the remainder,
except in terms of the suspension of treatment with ACE
inhibitors. At the final examination (at five years), the
LVEF was significantly lower among the patients in
whom ACE inhibitor treatment had been suspended (47
[12%] compared to 57 [11%]; P=.002).

DISCUSSION

The long-term progress of patients with chronic dilated
cardiomyopathy is well known, and there is much

| TABLE 1. Demographic, Clinical and the Most Important Treatment Characteristics of the Patients in Whom ACE Inhibitor Treatment Was Suspended or Continued |
|-----------------|------------------|
| Age (years)     | No ACEI n=15     | With ACEI n=20 |
| males           | 23 (12)          | 24 (13)        |
| NYHA class I    | 15 (100%)        | 20 (100%)      |
| Previous LVEF   | 56 (8%)          | 57 (8%)        |
| Atrial fibrillation | 2 (13%)      | 3 (15%)        |

LVEF: left ventricular ejection fraction; ACEi: angiotensin converting enzyme inhibitors; NYHA: New York Heart Association.
Anguita-Sánchez M et al. Should Angiotensin-Converting Enzyme Inhibitors Be Continued Over the Long Term in Patients Whose Left Ventricular Ejection Fraction Normalizes After an Episode of Acute Myocarditis?

Evidence regarding the need for their chronic treatment with ACE inhibitors and beta-blockers. However, the natural history of patients with left ventricular systolic dysfunction due to myocarditis is less well known. A large percentage of these patients may see their LVEF normalize after the initial period of dysfunction, but it is unknown whether ACE inhibitors should be administered over the long term or even indefinitely. The present results suggest that up to one third of patients in whom ACE inhibitor treatment is suspended could suffer another episode of heart failure, while such events are rare in patients who continue with this treatment (only 5% suffered a new episode over the five year experimental period). Similarly, the LVEF was significantly lower at five years among those who had ceased to take ACE inhibitors. This might indicate that it is better to continue with these drugs after an initial episode of acute myocarditis even when progress is favorable. The mechanism via which ACE inhibitors provide their benefit in these patients is not well understood although several suggestions have been made, including their modulatory effect on the neurohormonal axis, the inhibition of fibrosis and the remodeling of the left ventricle, and the reduction in the number of small blood vessel spasms.

The present study has a number of limitations; it was observational and non-randomized, and the study population was small (due to the infrequency of this health problem). The decision to suspend treatment with ACE inhibitors was taken by the clinician normally in charge of each patient, and this could have originated some bias. However, the characteristics of both groups of patients were identical, as shown in Table, which reduces the likelihood of this. Given the time when the initial study was performed, no patient was administered beta-blockers. It is also possible that some of these patients did not suffer true myocarditis given the diagnostic criteria followed; some could have suffered other uncommon problems such as apical ballooning. Although the incidence of new heart failure was greater among those who had ceased to take ACE inhibitors, these events were rarely serious; no patient died, none needed to be readmitted to hospital, and all progressed well after the reintroduction of these drugs. Despite these limitations, the present results indicate that the suspension of ACE inhibitors may be associated with poorer progress and a reduction in the LVEF in this kind of patient. It would be interesting to determine which patients are at greater risk of suffering a deterioration in their LVEF after the suspension of ACE inhibitors. A randomized study with a larger numbers of patients will probably be required to confirm the present findings.

REFERENCES