Among patients undergoing heart transplantation, a fundamental clinical concern is the risk of rejection of the new organ. Although modern immunosuppressive regimens have reduced the incidence of rejection substantially, about one quarter of recipients will still have a rejection episode requiring treatment during the first year after transplantation.\(^1\) Acute rejection is the cause of 12% of deaths occurring between 1 month and 1 year after transplantation.\(^1\)

There is no established noninvasive marker of rejection available for heart-transplant recipients; instead they must undergo serial endomyocardial biopsies with histologic evaluation of myocardial tissue to monitor for rejection. Endomyocardial biopsy is an invasive procedure that is associated with a small but potentially clinically important risk of complications,\(^2,3\) as well as with varying degrees of pain and anxiety for patients.

The inconvenience and potential risks of endomyocardial biopsy have led investigators to consider and evaluate a long list of possible noninvasive approaches to the detection of cardiac allograft rejection. Cardiovascular magnetic resonance imaging,\(^4\) intramyocardial electrogram analysis,\(^5\) myocardial strain-rate imaging,\(^6\) antimyosin scintigraphy,\(^7\) and lymphocyte-function assays\(^8\) are among the many tests that have been shown to have a significant correlation with histologic evidence of rejection. However, none of these methods have been tested in a clinical trial to determine whether relying on such a screening assay for monitoring rejection is as safe as performing endomyocardial biopsies, with respect to clinical outcomes.

The Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial, the results of which are reported in this issue of the Journal,\(^9\) is therefore an important advance in the assessment of noninvasive methods for monitoring rejection after heart transplantation. This trial evaluated a commercially available gene-expression profiling test called the AlloMap, which had previously been correlated with results of endomyocardial biopsy,\(^10\) in a randomized comparison with routine endomyocardial biopsies for monitoring rejection. Patients who had received a heart transplant at
least 6 months previously were randomly assigned to either routine biopsies according to standard practice or to routine gene-expression profiling, with a biopsy performed only if the noninvasive assay score was above a prespecified threshold.

The end point of the trial was not the number of episodes of rejection detected (which would inevitably be fewer in the noninvasive-screening group), but rather the clinical consequences of greatest concern — allograft dysfunction, death, or retransplantation. At 2 years, the cumulative rate of this composite end point was 14.5% with gene-expression profiling and 15.3% with endomyocardial biopsies. The prespecified statistical analysis was a noninferiority analysis, which specified that the upper bound of the 95% confidence interval for the primary outcome measure could not be greater than 2.054 for noninferiority to be demonstrated. Since the trial data showed a hazard ratio of 1.04 and a 95% confidence interval of 0.67 to 1.68, the criterion for noninferiority was satisfied. This result was achieved with 0.5 cardiac biopsies performed per patient-year of follow-up in the gene-profiling group, as compared with 3.0 biopsies per patient-year in the biopsy group.

Given these results, should the AlloMap test replace routine endomyocardial biopsies for monitoring rejection in heart-transplant recipients? It is certainly very encouraging to learn that serious adverse clinical events were no more frequent when this diagnostic strategy was used than when endomyocardial biopsies were routinely performed, and many patients would enthusiastically embrace an approach that requires fewer biopsies. However, there are a number of limitations to the IMAGE trial, which have been appropriately acknowledged by the authors.

First, the authors enrolled only patients who had undergone transplantation at least 6 months previously. In so doing, they selected a population that was at lower risk for rejection, since that risk is highest in the first 3 months after surgery and declines rapidly thereafter. In addition, only 20% of potentially eligible patients were enrolled, presumably in many cases because the patient's own physicians chose not to include higher-risk candidates. These constraints may have been necessary to ensure equipoise with respect to the two clinical strategies under comparison. However, the consequence is that the patient cohort studied is not fully representative of the larger population of heart-transplant recipients.

Second, the noninferiority margin chosen was quite wide. The actual 95% confidence interval is consistent with as much as a 68% increase in risk with the gene-expression profiling strategy. Such a potential risk might legitimately give pause to a transplantation physician before he or she chooses to adopt the noninvasive monitoring approach. Furthermore, the primary end point of the trial undoubtedly included some events that would not be associated with rejection risk, since not all cases of graft dysfunction, death, or retransplantation are due to rejection. This further reduced the power of the trial to detect a difference between the two surveillance strategies.
The most notable implication of the IMAGE trial may in fact be the evidence it offers that calls into question the importance of any form of routine screening for the early detection of rejection in the longer term after transplantation. Of the 34 rejection episodes identified in the gene-profiling group in the trial, only 6 were detected solely on the basis of the gene-expression profiling test. All the other episodes were associated with clinical manifestations of heart failure or echocardiographic evidence of allograft dysfunction. This observation suggests that, even if rejection is not identified until graft dysfunction is present, the clinical outcomes may not be substantially worse than when rejection is detected early. This conclusion has already been reached by some centers, which have stopped performing endomyocardial biopsies on a routine basis between 1 and 5 years after transplantation. In an analysis by the Cardiac Transplant Research Database Group, there was no evidence that continuing to perform biopsies beyond 5 years was associated with a lower risk of rejection with hemodynamic compromise or better survival.12

Perhaps it is time to perform a randomized trial that compares a strategy of continuing endomyocardial biopsies indefinitely with that of discontinuing routine endomyocardial biopsies at some specified interval. Alternatively, perhaps centers should begin to use the available data to individualize biopsy schedules and other surveillance techniques on the basis of specific known determinants of risk, such as female sex, young age, and history of rejection.13 The IMAGE trial suggests that there may be room for such innovations in the often tradition-bound practice of transplantation cardiology.

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References


