Acute Exacerbations in Idiopathic Pulmonary Fibrosis

TO THE EDITOR: The data provided by Martinez and colleagues (1) are a further example of the merits of offering treatment to patients with idiopathic pulmonary fibrosis (IPF) only as part of a therapeutic trial. Although the large international study of interferon-γ use in IPF was mostly negative, the data gleaned from the placebo group are critical to our understanding of the natural history of this fatal condition (2). Needless to say, the information provided raises many additional questions. Researchers are increasingly recognizing acute exacerbations of IPF as an important clinical entity. I would be interested in learning whether it is possible to identify which patients are most at risk for an exacerbation on the basis of a physiologic assessment (3). For example, are patients with advanced disease (dissolving capacity of carbon monoxide [DLCO] of <40%) more predisposed to acute exacerbations than patients with limited disease on the basis of an estimation of their gas transfer? This data would be important for planning future studies of IPF management.

Second, data have been published that suggest an association between interferon-γ use and acute deteriorations (4). The data provided by Martinez and colleagues may refute these findings by comparing the incidence of acute exacerbations in the treatment group with that observed in the control group. For example, if the incidence of acute exacerbations was the same or less in the treatment group, such data would seem to rule out interferon-γ as a cause of deterioration. Therefore, the previously suggested association may in fact be coincidental; the acute exacerbations are more related to the degree of physiologic impairment of the disease than to the drug used to treat the condition.

Seamus P. Crowley, MD
Peter Kelly, MD, MS
Jim J. Egan, MD
Mater Misericordiae Hospital
Dublin 7, Ireland

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Drs. Crowley, Kelly, and Egan raise several important points regarding our recent report that identified a high incidence of rapidly progressive pulmonary disease in the placebo group of a multicenter trial of interferon-γ1b in patients with IPF. The identification of patients who succumbed to a rapid, fatal deterioration versus those who did not provides important, clinically relevant information.

Examination of baseline characteristics of patients who died abruptly of IPF-related causes and those of patients who died following an IPF-related subacute deterioration revealed a similar baseline mean predicted FVC (64% [SD, 12%] vs. 60% [SD, 12%]; P = 0.29) and mean DLCO (33% [SD, 6%] vs. 31% [SD, 7%]; P = 0.43) in both groups. The overall incidence of acute deterioration leading to death was similar in patients with a baseline predicted DLCO of less than 40% (10.5%) and in those with a baseline predicted DLCO of greater than 40% (11.1%). If we examine only the IPF-related acute deteriorations that led to death, the incidence was a bit higher in patients with a baseline predicted DLCO that was less than 40% than in those whose DLCO was greater (10.5% vs. 5.6%). By using methodology that was recently published (1), we found that the distribution of typical, basilar-predominant honeycomb changes in those patients who died after acute declines was similar to that seen in patients with subacute deterioration (87% vs. 94%; P = 0.60). In addition, 87% of patients with acute progression had a mean high-resolution extent score of greater than 0 compared with 100% of patients with subacute deterioration (P = 0.23). In abstract form, we have characterized features that predicted the risk for death in the placebo group (2). In these preliminary analyses, we found that a decrease in FVC of more than 10%; the emergence of respiratory symptoms requiring hospitalization; and an increase in the University of California, San Diego, Shortness of Breath Questionnaire score of more than 10 points were associated with an increased risk for death within 3 months.

Interferon-γ1b has been explored as a possible novel therapeutic agent in IPF (3, 4). Results of the phase 3 trial from which the placebo cohort was drawn suggested that the use of interferon-γ1b may lead to improved survival (4). At the 2005 European Respiratory Society meeting in Copenhagen, Denmark, researchers presented data on the incidence and timing of serious respiratory adverse events after the initiation of therapy with interferon-γ1b. Patients (n = 362) from 2 randomized, double-blind, placebo-controlled trials and 1 extension study were analyzed. The number of patients with serious respiratory adverse events throughout the study was similar in the interferon-γ1b and placebo groups in both of the randomized trials. These data were supported by the findings of the open-label extension study, which failed to show any increased risk for serious respiratory adverse events after recent initiation of treatment (5). An additional placebo-controlled study that is currently ongoing seeks to better define the effect of interferon-γ1b on overall mortality rates and the timing of death in well-characterized patients with mild to moderate IPF. The results of this study should further clarify the natural history and characteristics of mortality in patients with IPF and the effect of interferon-γ1b in this population.

Fernando J. Martinez, MD, MS
University of Michigan
Ann Arbor, MI 48109

Potential Financial Conflicts of Interest: Consultancies: F.J. Martinez (InterMune, Inc.).
Quality of Care for Vulnerable Older Patients

TO THE EDITOR: In a recent meeting of our fellows and departmental faculty, we discussed the findings of Higashi and colleagues (1). We were considerably excited because we are committed to quality care for our frail older patients. To our surprise, the analyses as presented did not support the conclusions.

The authors state that for 8 of the 9 quality indicators that they defined, “patients who received recommended care were less likely to die than those who did not receive such care (Table 2).” Only 1 of these 9 quality indicators was significant—the exact opposite of the text. Pneumococcal vaccine lowered the risk for death by 54% whereas all the others did not alter risk. Figure 1, which compared high-quality and low-quality care groups, showed a clear separation only after 800 days. During the first 400 days, the lines were indistinguishable. The authors used the Vulnerable Elders Survey-13 (VES-13) to create the sample. According to the survey’s creators (2), the VES-13, which takes age into consideration, was a strong predictor of survival, as expected. We share Dr. Garrett and colleagues’ strong argument for palliative care medicine. By sorting out robust older adults from frail ones, we will be able to improve the quality of care for all.

Dr. Garrett and colleagues state that there is a lack of association between the Assessing Care of Vulnerable Elders (ACOVE) quality indicators (3) and survival in this sample makes a strong argument for palliative care medicine. By sorting out robust older adults from frail ones, we will be able to improve the quality of care for all.

Stephanie L. Garrett, MD
James G. O’Brien, MD
Toni P. Miles, MD, PhD
University of Louisville
Louisville, KY 40202

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We interpret the findings very differently from the way Dr. Garrett and colleagues did, although we agree with their conclusion that there is a strong argument for palliative medicine for many of the patients in the study sample. Many of the quality indicators in the ACOVE measurement set focused on pain and end-of-life care.

Dr. Garrett and colleagues state that there is a lack of association between our quality measurement and survival, yet the analyses in the article demonstrate a strong relationship. Their concern that only 1 of 9 of the most prevalent quality indicators (in Table 2) demonstrated a statistically significant relationship between receiving the care process and survival misses the point; these ancillary analyses, which are statistically underpowered and unadjusted, were presented only to provide insight into potential mechanisms of the relationship between process and outcome. We focused on the direction of the point estimates by showing that the relative risk for death for those who passed the quality indicators was less than 1.0 in 8 of the 9 quality indicators.

Dr. Garrett and colleagues expressed concerns about our use of the VES-13 to select community-dwelling vulnerable older persons, and they were interested in the age distribution within our sample. Furthermore, they were concerned about the relationship between age and survival in our cohort. There were 135 persons who were 85 years of age or older, 79 of whom had VES-13 scores of 5 or less. The VES-13, which takes age into consideration, was a strong predictor of survival, as expected. We share Dr. Garrett and colleagues’ excitement about our findings and their commitment to quality care for older patients.

Takahiro Higashi, MD, PhD
Kyoto University Department of Epidemiology and Healthcare Research
Kyoto 606-8501, Japan

References
5. Loutit JS, Saffin S, Suzuki S, Bradford WZ. Serious adverse events (SAEs) of the respiratory tract in patients with idiopathic pulmonary fibrosis (IPF) treated with interferon-gamma-1b (IFN-gamma 1b) in three trials. Eur Respir J. 2005;26:336s.
The Pittfalls of Introducing Electronic Medical Records

TO THE EDITOR: The perspective expressed by Dr. Baron and his partners (1) demonstrated the pitfalls associated with the difficult task of implementing an electronic medical record (EMR) system. Our group has had a different experience. Mercy Medical Group, owned by the Sisters of Mercy Health System, comprises 160 physicians and includes internists, family practitioners, pediatricians, and women’s health practitioners. With the financial backing of the health system, we researched several EMR vendors and chose Misys EMR (Misys Healthcare Systems, Raleigh, North Carolina) because we had been using their practice management system, which interfaced with their EMR system. Having the health system’s support and financing was a significant advantage that an individual group of physicians starting an EMR system does not have.

Our pilot group of 4 general internists went live in March 2003. The physicians and staff each received about 8 hours of training before going live and continued to receive support afterward. Misys provided workflow recommendations, training, and support in our early development of EMR implementation. We redesigned our workflow and had excellent support from the company’s information technology department and the EMR project managers throughout this period. To better familiarize themselves with the EMR, the physicians were using the system for office visits and printing the notes for documentation in the paper charts for a few weeks before going live. The physicians also spent time entering patient data into the EMR for several weeks before going live. Entering these data is a major hurdle for making the transition to an EMR, and we have not been able to find a way around it.

We reduced our patient appointments by 50% when we went live; over the next 2 weeks, we were able to increase back to our usual patient load. Our staff was somewhat skeptical at first, but having an effective office manager made the transition easier and now neither the physicians nor the staff would want to return to paper charts. The EMR has allowed us to improve our revenue slightly and foresee a few more patients per day. We are working to improve our auditing capabilities and to move forward with pay-for-performance programs.

A complex project of this magnitude has had its frustrating moments. We have experienced power outages and problems with our servers, which our support staff has been quick to correct. The transition would have been much more difficult without their assistance and rapid response. Our goal of making our EMR compatible with our Quest Diagnostics interface was also a difficult process that our support staff was able to make a reality. Misys has also been very receptive to our requests to improve the EMR system, and each version improves its functionality. We have 35% of our physicians using the EMR system, and we add another practice every 3 weeks.

We applaud Dr. Baron and his partners for implementing an EMR and for enduring a difficult transition period. We feel that our experience was less painful because of the financing by our health system and the support provided by Misys and our information technology and EMR staff. Our preparation before going live, which included workflow redesign, training, and data entry, also helped to ease the transition.

Neil Wenger, MD, MPH
RAND
Santa Monica, CA 90407

Paul Shokelle, MD, PhD
Greater Los Angeles Veterans Affairs Healthcare System
Los Angeles, CA 90073

Potential Financial Conflicts of Interest: None disclosed.

Presentation of Diagnostic Test Accuracy

TO THE EDITOR: We agree with Dr. Puhan and his colleagues (1) that it is essential for physicians to interpret the real value of diagnostic testing to confirm clinical suspicions so that a better practice of medicine can occur. After reading their conclusions, we believe that replication of their results is needed, perhaps with a few modifications. Our suggestions are not intended to diminish the findings of what we consider to be an excellent study.

Although a table for the clinical vignettes was provided, it was not clear if equations to calculate illness probability changes were provided to surveyed physicians. Perhaps physicians are less likely to remember complex equations that are not commonly used in clinical practice. If equations were not available to the physicians, then the authors could have been testing knowledge and recall of biostatistical methods rather than the ability to calculate post-test probability.

Although the researchers were able to determine if actual calculations had been made, we speculate that the authors were not able to determine the reasons why participants were not able to provide the correct post-test probability. Was it because the physicians simply did not know how to do the calculations (and therefore they guessed the answer), or was it because they did not agree with the logic of the diagnostic testing? If the latter is true, then it is likely that the physicians based their answers on what they thought the post-test probability would be regardless of the testing.

Regarding the survey instrument, we suggest that future investigations should avoid mixing test results with the findings of physical examinations or medical histories. The aim of this suggestion is simply to avoid confusing scenarios that could possibly influence the results of any post-test probability calculations. Furthermore, to reduce unexplained errors, we recommend selecting a team of medical experts who are familiar with the medical conditions of interest to help design and validate the instrument before implementation. Similarly, it would be wise to test the validity and reliability of the instrument before administering it to a survey group. Consequently, we applaud Dr. Puhan and his colleagues for implementing an EMR and for enduring a difficult transition period. We feel that our experience was less painful because of the financing by our health system and the support provided by Misys and our information technology and EMR staff. Our preparation before going live, which included workflow redesign, training, and data entry, also helped to ease the transition.

TO THE EDITOR: The perspective expressed by Dr. Baron and his partners (1) demonstrated the pitfalls associated with the difficult task of implementing an electronic medical record (EMR) system. Our group has had a different experience. Mercy Medical Group, owned by the Sisters of Mercy Health System, comprises 160 physicians and includes internists, family practitioners, pediatricians, and women’s health practitioners. With the financial backing of the health system, we researched several EMR vendors and chose Misys EMR (Misys Healthcare Systems, Raleigh, North Carolina) because we had been using their practice management system, which interfaced with their EMR system. Having the health system’s support and financing was a significant advantage that an individual group of physicians starting an EMR system does not have.

Our pilot group of 4 general internists went live in March 2003. The physicians and staff each received about 8 hours of training before going live and continued to receive support afterward. Misys provided workflow recommendations, training, and support in our early development of EMR implementation. We redesigned our workflow and had excellent support from the company’s information technology department and the EMR project managers throughout this period. To better familiarize themselves with the EMR, the physicians were using the system for office visits and printing the notes for documentation in the paper charts for a few weeks before going live. The physicians also spent time entering patient data into the EMR for several weeks before going live. Entering these data is a major hurdle for making the transition to an EMR, and we have not been able to find a way around it.

We reduced our patient appointments by 50% when we went live; over the next 2 weeks, we were able to increase back to our usual patient load. Our staff was somewhat skeptical at first, but having an effective office manager made the transition easier and now neither the physicians nor the staff would want to return to paper charts. The EMR has allowed us to improve our revenue slightly and foresee a few more patients per day. We are working to improve our auditing capabilities and to move forward with pay-for-performance programs.

A complex project of this magnitude has had its frustrating moments. We have experienced power outages and problems with our servers, which our support staff has been quick to correct. The transition would have been much more difficult without their assistance and rapid response. Our goal of making our EMR compatible with our Quest Diagnostics interface was also a difficult process that our support staff was able to make a reality. Misys has also been very receptive to our requests to improve the EMR system, and each version improves its functionality. We have 35% of our physicians using the EMR system, and we add another practice every 3 weeks.

We applaud Dr. Baron and his partners for implementing an EMR and for enduring a difficult transition period. We feel that our experience was less painful because of the financing by our health system and the support provided by Misys and our information technology and EMR staff. Our preparation before going live, which included workflow redesign, training, and data entry, also helped to ease the transition.

Neil Wenger, MD, MPH
RAND
Santa Monica, CA 90407

Paul Shokelle, MD, PhD
Greater Los Angeles Veterans Affairs Healthcare System
Los Angeles, CA 90073

Potential Financial Conflicts of Interest: None disclosed.

Presentation of Diagnostic Test Accuracy

TO THE EDITOR: We agree with Dr. Puhan and his colleagues (1) that it is essential for physicians to interpret the real value of diagnostic testing to confirm clinical suspicions so that a better practice of medicine can occur. After reading their conclusions, we believe that replication of their results is needed, perhaps with a few modifications. Our suggestions are not intended to diminish the findings of what we consider to be an excellent study.

Although a table for the clinical vignettes was provided, it was not clear if equations to calculate illness probability changes were provided to surveyed physicians. Perhaps physicians are less likely to remember complex equations that are not commonly used in clinical practice. If equations were not available to the physicians, then the authors could have been testing knowledge and recall of biostatistical methods rather than the ability to calculate post-test probability.

Although the researchers were able to determine if actual calculations had been made, we speculate that the authors were not able to determine the reasons why participants were not able to provide the correct post-test probability. Was it because the physicians simply did not know how to do the calculations (and therefore they guessed the answer), or was it because they did not agree with the logic of the diagnostic testing? If the latter is true, then it is likely that the physicians based their answers on what they thought the post-test probability would be regardless of the testing.

Regarding the survey instrument, we suggest that future investigations should avoid mixing test results with the findings of physical examinations or medical histories. The aim of this suggestion is simply to avoid confusing scenarios that could possibly influence the results of any post-test probability calculations. Furthermore, to reduce unexplained errors, we recommend selecting a team of medical experts who are familiar with the medical conditions of interest to help design and validate the instrument before implementation. Similarly, it would be wise to test the validity and reliability of the instrument before administering it to a survey group. Consequently, we applaud Dr. Puhan and his colleagues for implementing an EMR and for enduring a difficult transition period. We feel that our experience was less painful because of the financing by our health system and the support provided by Misys and our information technology and EMR staff. Our preparation before going live, which included workflow redesign, training, and data entry, also helped to ease the transition.

Neil Wenger, MD, MPH
RAND
Santa Monica, CA 90407

Paul Shokelle, MD, PhD
Greater Los Angeles Veterans Affairs Healthcare System
Los Angeles, CA 90073

Potential Financial Conflicts of Interest: None disclosed.

Reference

any conclusions or generalizations about research findings would be sound.

Finally, for the benefit of readers, researchers who wish to publish similarly designed studies should consider the addition of detailed information about the methods and procedures, particularly the participant instructions and a copy of the actual survey instrument.

Mike Broce, BS
Bernardo Reyes, MD
CAMC Institute
Charleston, WV 25304

Potential Financial Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: Puhan and colleagues (1) deserve praise for their creative assessment of how well physicians interpret diagnostic test results, but I disagree with their conclusion that likelihood ratios are no more informative than sensitivity and specificity. The authors asked clinicians to estimate the post-test probabilities of various conditions by using pretest probabilities and diagnostic test results. The operating characteristics of each diagnostic test were provided in terms of likelihood ratios, sensitivity and specificity, or a graphic display. There are 2 problems with this approach.

First, familiarity with the method is required. When I finished medical school in the 1990s, I had been taught to think in probabilities (sensitivity, specificity, and predictive values). In contrast, I was taught to think in odds (likelihood ratios) only later in my career, during biostatistical training. To assess the relative merits of likelihood ratios (versus sensitivity and specificity) on the basis of how well clinicians know how to use them is like determining the utility of the metric system on the basis of whether New Englanders can more accurately estimate the length of their strides in inches versus centimeters.

Second, the scenarios that the authors formulated failed to expose the most serious conceptual error surrounding sensitivity and specificity. Clinicians are not often taught that both sensitivity and specificity are needed to assess post-test probability (whether the test results are positive or negative). Indeed, many medical students are taught that high sensitivity “rules out” a diagnosis if the test result is negative and that high specificity “rules in” the diagnosis when the test result is positive. The limitations of this rule of thumb are exposed by an inexpensive and quite versatile laboratory test that I have created. It has 97.2% sensitivity for pulmonary emboli, myocardial infarctions, and even erectile dysfunction. It is called the 2-dice test. I roll 2 dice, each of which has 6 sides, and add the values showing. Anything 3 or higher is a positive test result. The problem is that the specificity is only 2.8%. Had Puhan and colleagues presented a hypothetical scenario in which a test had 97.2% sensitivity and 2.8% specificity, the pretest probability of disease was 50%, and the test result was negative, I suspect that many of the physicians would have deemed the diagnosis very unlikely. In contrast, present the same physicians with a test that has a negative likelihood ratio of 1.0 and they will not be fooled. These same physicians are out there misinterpreting negative results of D-dimer tests in critically ill patients (2).

Daniel J. Brotman, MD
Johns Hopkins University Hospital
Baltimore, MD 21287

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Mr. Broce and Dr. Reyes state that it remains unclear how the surveyed physicians derived post-test probabilities. They wondered whether we provided the relevant equations and whether we recorded if participants calculated or guessed post-test probabilities. In fact, we did neither. Therefore, we could not determine how the physicians arrived at their post-test probabilities. However, our experience and research have shown us that most physicians do not formally calculate post-test probabilities; instead, they use quantitative information about a test’s informativeness in an inexact way (1, 2). Along the same line, we developed the inexact numerical graphical format. The setting of our trial, a lecture hall at a continuous medical education conference, was not conducive to studying the physicians’ cognitive processes. However, we would welcome the opportunity to read reports of any studies investigating physicians’ cognitive processes when they are confronted with quantitative information about a test’s informativeness.

Dr. Brotman argues that our study did not test if the likelihood ratio (equal to 1) was the superior measure of association at extreme combinations of sensitivities and specificities (for example, a sensitivity of 0.97 and a specificity of 0.03). His hypothesis might be correct, but these extreme values of sensitivity and specificity are rare in commonly encountered diagnostic situations. We decided to present vignettes of more common clinical scenarios. Nevertheless, vignettes 1 and 4, which most closely resembled the situation that Dr. Brotman had preferred (vignette 1 had a sensitivity of 0.93 and specificity of 0.45 [likelihood ratio, 1.7]; vignette 4 had a sensitivity of 0.40 and a specificity of 0.79 [likelihood ratio, 0.8]), yielded only negligible differences between the 2 numerical formats on post-test probability estimates.

We agree that relevant experts should be involved in designing survey instruments before they administer them. Therefore, we tested and revised our vignettes with the help of 21 interns. We cannot refute the idea that a more sophisticated development process might have resulted in better vignettes. We agree that the vignettes’ test–retest reliability could, and perhaps should, have been evaluated before use. However, we are not sure if the validity of the vignettes can be measured by any other means than through the eyes of experienced clinicians.

We welcome the suggestions for further studies that factor in the additional methodologic aspects highlighted by Mr. Broce and Drs. Reyes and Brotman. Or, in the spirit of Karl Popper: Design carefully and aim to refute so that you may corroborate convincingly.
Thyrotoxicosis as a Risk Factor for Pulmonary Arterial Hypertension

TO THE EDITOR: Although Rubin and associates (1) pointed out the importance of assessing patients with pulmonary arterial hypertension (PAH) for underlying autoimmune–collagen vascular disease, the need to assess for thyroid dysfunction and autoimmune thyroid disease was not addressed. Previous studies have suggested a link between primary pulmonary hypertension and autoimmune thyroid disease (2). More recently, it has become apparent that thyrotoxicosis is itself an important risk factor for PAH (3, 4). This may be partly due to the hemodynamic effects of hyperthyroidism because biochemical improvement in thyroid function following treatment has been proven.

Regardless of whether thyroid disease and PAH share a common pathogenic mechanism, their frequent coexistence is important to recognize; thyroid disease produces cardiovascular stresses that are poorly tolerated in the setting of PAH and should therefore be treated aggressively. However, β-blockers, which are commonly used as adjunct therapy in hyperthyroidism, may precipitate worsening of right ventricular dysfunction and should be avoided or used very cautiously.

Lewis J. Rubin, MD
University of California, San Diego
La Jolla, CA 92039

David B. Badesch, MD
University of Colorado Health Sciences Center
Denver, CO 80262

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We agree with Drs. Ma and Chow that there is some justification for screening patients with PAH for thyroid dysfunction. We were among the first to make the observation that thyroid abnormalities might occur with increased frequency in patients with PAH (1). In that report, we speculated that there might be a common underlying autoimmune disorder. The concept that antithyroid antibodies could play a role in the pathogenesis of PAH is indeed quite intriguing, and there have been several subsequent reports of hypothyroidism and hyperthyroidism occurring in patients with pulmonary hypertension (2–5), although a causal relationship has not been proven.

Regardless of whether thyroid disease and PAH share a common pathogenic mechanism, their frequent coexistence is important to recognize; thyroid disease produces cardiovascular stresses that are poorly tolerated in the setting of PAH and should therefore be treated aggressively. However, β-blockers, which are commonly used as adjunct therapy in hyperthyroidism, may precipitate worsening of right ventricular dysfunction and should be avoided or used very cautiously.

Lewis J. Rubin, MD
University of California, San Diego
La Jolla, CA 92039

David B. Badesch, MD
University of Colorado Health Sciences Center
Denver, CO 80262

Potential Financial Conflicts of Interest: None disclosed.

References
5. Kashyap AS, Kashyap S. Thyroid disease and primary pulmonary hypertension
Liver Transplantation in HIV-Seropositive Individuals

TO THE EDITOR: We were pleased that our recent paper (1) concerning liver transplantation in HIV-infected individuals was chosen for the 2005 Update in Gastroenterology and Hepatology (2), but we would like to clarify a few points about our paper and this evolving field.

Contrary to the review by Drs. Koretz and Lipman, this was a prospective study of consecutively enrolled HIV-seropositive liver transplant recipients who underwent the procedure according to the same listing criteria as HIV-seronegative recipients. We felt compelled to carry out this study because 1) significant advances had occurred in the area of highly active antiretroviral therapy (HAART), 2) HIV-seropositive individuals were surviving with AIDS only to die of end-stage liver disease (3), and 3) our past studies had suggested that liver transplantation was unsafe because of the immunodeficiency associated with antirejection immunotherapy and with HIV infection (before the advent of HAART) (4).

We therefore tested the hypothesis that HIV-seropositive transplant recipients who are treated with HAART have similar survival rates to HIV-seronegative recipients. Patients were accepted for the study on the basis of the standard listing criteria that are used for HIV-seronegative individuals as well as evidence of the patient’s adherence and responsiveness to HAART. It should be noted that HIV-seropositive transplant recipients had an average Model for End-Stage Liver Disease (MELD) score of 15, similar to the average score of 16 observed among HIV-seronegative patients who received transplants in the United States (5).

Furthermore, our findings were the impetus for the Solid Organ Transplant in HIV Study (sponsored by the National Institute of Allergy and Infectious Diseases), which will determine the safety and efficacy of liver transplantation in individuals with HIV infection. If our findings are confirmed in this multicenter study, then we believe HIV infection should no longer be an absolute contraindication to transplantation. While immunosuppression continues to be associated with significant morbidity in both HIV-seropositive and HIV-seronegative transplant recipients, it should be recognized that hepatitis B virus infection was also a relative contraindication to liver transplantation until the recent development of new antiviral agents.

Finally, decisions regarding organ allocation in HIV infection that are made on the basis of cost or utility are invariably flawed; the same argument could be made regarding organ allocation to individuals with hepatitis C virus infection, hepatocellular carcinoma, diabetes, or chronic pulmonary disease or to those within a particular age bracket or having a particular MELD score. Therefore, the conclusion by Drs. Koretz and Lipman that transplantation is less effective or less warranted in HIV-seropositive individuals is simply incorrect and unjustified.

Margaret V. Ragni, MD, MPH
Steven H. Belle, PhD
Kyung Ah Im, BS
University of Pittsburgh
Pittsburgh, PA 15260

Potential Financial Conflicts of Interest: None disclosed.

References
4. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis. 2001;183:1112-5. [PMID: 11237838]

IN RESPONSE: We thank Dr. Ragni and colleagues for clarifying the prospective nature of their study (1). This was not apparent to us from their Methods section, which stated that “24 subjects with HIV infection and [end-stage liver disease] who fulfilled standard listing criteria for liver transplantation underwent [orthotopic liver transplantation] at 5 institutions.”

Dr. Ragni and colleagues state that there were no differences between the MELD scores of their patients and those of the patients who were HIV-seronegative. However, in the accompanying editorial (2), Dr. Fishman cited a 2002 report by the United Network for Organ Sharing that indicated that the median MELD score during the past year in patients without acute hepatic failure was 22.16. Dr. Fishman also noted that, in regions with severe organ shortages, transplantation could not occur until the MELD score was in the range of 25 to 35.

Dr. Ragni and associates concluded that the survival of HIV-seropositive liver transplant recipients does not differ from that of HIV-seronegative ones. However, the length of follow-up in their 24 recipients was limited; only 3 were followed for at least 36 months. The 5-year survival rate was only 36%, compared with 71% in the HIV-seronegative cohort. Even if this difference was not statistically
significant, the numbers are small and the arithmetic difference is large. Failure to prove a difference does not necessarily guarantee the presence of equivalence.

For us, the point of disagreement relates to applicability of the findings in the world of transplantation. As a society, we will have to make decisions regarding resource utilization for health care because those resources (money and organs) are not unlimited. If we cannot use cost and efficacy, what are we to use? Even if we accept the figure of $50 000 per life-year saved (and that figure, if applied to the entire population, is higher than the gross domestic product), organ transplantation in anybody is arguably too expensive. If 2 otherwise similar patients (differing only in HIV status) are competing for 1 available organ, and even if the long-term outcomes are the same, the additional cost of the HIV therapy will add more expense to the post-transplantation care (the authors’ data certainly cannot be interpreted to infer that the post-transplantation course of the HIV-seropositive individual is better). If health care resources were infinite, the only issue would be to avoid harm. Because resources are limited, we have to be prepared to make judgments about where to do good.

Ronald L. Koretz, MD
Olive View—University of California Los Angeles Medical Center
Sylmar, CA 91342

Timothy O. Lipman, MD
Veterans Affairs Medical Center
Washington, DC 20422

Potential Financial Conflicts of Interest: None disclosed.

References

Savings from Canadian Internet Pharmacies Are Limited

TO THE EDITOR: After comparing prices at American and Canadian Internet pharmacies, Quon and colleagues (1) concluded that “Americans purchasing brand-name medications from Canadian Internet pharmacies can realize substantial savings.” Although this is undoubtedly true for a few individuals, it does not address the needs of the two thirds of Americans who feel drug prices are unreasonably high. As the authors point out, reimportation accounts for less than 1% of the U.S. market; however, even this small amount has led to rapidly rising prices at Canadian pharmacies over a 6-month period.

The companies that manufacture the drugs would rather cut off all supply to 30 million Canadians than let Canada set the prices for 300 million Americans. Pharmaceutical companies have already begun limiting sales to Canada, and Merck announced in January that it would no longer sell to Canadian pharmacies that export to the United States (2). The Canadian Health Minister, aware of the threat to Canadian supplies, last summer proposed legislation to prohibit bulk exports to U.S. citizens without prescriptions from Canadian physicians (3).

Even though most Americans favor Canadian-style price controls, industry lobbying makes the passage of such controls unlikely. An American-style alternative exists. In extending prescription drug coverage to Medicare patients, Congress missed an opportunity to lower drug prices by allowing the government to negotiate prices on behalf of 40 million Medicare beneficiaries. The Veterans Administration routinely obtains discounts of 16% to 41% by using this strategy (4). Instead of turning to the Canadian government to secure drug discounts for us, we should repeal the anticompetitive language in the current Medicare law.

Michael Rothberg, MD
Baystate Medical Center
Springfield, MA 01199

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We agree with Dr. Rothberg that Americans should not have to look north of the border to access more affordable medications. The underlying premise of our article was not to promote the purchase of Canadian pharmaceuticals but to quantify and highlight the differences in brand-name medication prices between the 2 countries. The average savings of 24% per unit that we cited should serve as a benchmark for Congress to target in lowering brand-name medication prices domestically for all Americans. Canadian-style strategies to lower medication prices, including price control through the Patented Medicines Price Review Board and the use of market-based competition through provincial drug reimbursement formularies, have proven to be effective. Of importance, Americans can look within their own borders to observe the benefits of drug coverage formularies. As Dr. Rothberg pointed out, this strategy has been used successfully by the Veterans Administration to lower medication prices for U.S. government employees (1). Congress will need to find creative ways to extend a formulary-based strategy to benefit low-income Americans who are without prescription drug coverage—ironically, the same individuals who pay the highest prices for their medications.
TO THE EDITOR: As an infectious disease specialist, I was surprised that 3 (20%) of the 15 articles that were cited in the recent Update in Cardiology (1) dealt with 1 specific drug, atorvastatin. Dr. Peter H. Stone, the author of the Update, claimed that he had no conflict of interest. However, with the vast number of drug studies and the intense competition in the cardiology field, I found 3 citations on atorvastatin to be remarkably disproportionate.

My simple search of PubMed for “PH Stone” and “atorvastatin” yielded 3 articles (2–4). The research for all of these articles was supported in part by unrestricted grants from Pfizer, the manufacturer of atorvastatin.

This is a major conflict of interest. In an Update presented at the College’s Annual Session and then published in Annals, Dr. Stone should have gone out of his way not to favor articles on the drug he has studied. There can be no excuse for 3 of 15 articles regarding cardiology-related subjects from 2004 to have atorvastatin in the title. Furthermore, I believe that it is purposely misleading (that is, dishonest) for Dr. Stone to indicate “none” when reporting his potential financial conflicts of interest.

Daniel M. Musher, MD
Baylor College of Medicine
Houston, TX 77005

IN RESPONSE: I acknowledge that I should have disclosed my potential conflicts of interest; I did not do so previously because, after careful thought, I considered that they were either outdated or insufficiently related to the content of my presentation to warrant inclusion. My 3 articles cited by Dr. Musher (1–3) as representing research studies supported by Pfizer were, in fact, all from a single study, the Vascular Basis for the Treatment of Myocardial Ischemia Study, which was funded by a National Institutes of Health Research Project (RO1) grant and by the National Heart, Lung, and Blood Institute. These 3 articles comprise the design manuscript (1), the primary end point manuscript (2), and a small database study (3). Only a small proportion of supplemental funding for that clinical trial was provided by Pfizer, and there had not been funding from Pfizer for that study for more than 2 years before I wrote the Update. Since that clinical trial was completed, my relationship with Pfizer has been minimal.

The year 2004 was indeed extraordinary for the field of cardiology because research published that year dramatically expanded the understanding of the “lipid hypothesis” and clarified the role of inflammation in the clinical and anatomic manifestations of coronary atherosclerosis. Specifically, statin studies that were published in 2004 were unique because they compared an intensive regimen of atorvastatin with a less intense regimen of another statin, thereby enabling an evaluation of comparative efficacy based on magnitude of lipid-lowering or the specific agent used. In contrast, earlier studies of the clinical benefit of individual statins used only placebo controls. The landmark atorvastatin studies that I cited for 2004 provided critical information concerning optimal goals of lipid-lowering (4) and critical data correlating anatomic improvement in coronary atherosclerosis from lipid-lowering with statins to the clinical benefit of lipid-lowering therapy with statins (5). The results from these 2 atorvastatin studies led to revised recommendations of lipid-lowering goals by the National Cholesterol Education Program’s Adult Treatment Panel III. A third innovative atorvastatin study expanded the role of lipid-lowering in primary prevention and was terminated prematurely because an interim analysis found a significant benefit in the active treatment group (6). The apparent disproportion of atorvastatin studies in 2004 was attributable to the fact that most of the year’s important studies of lipid-lowering strategies used atorvastatin.

My focus on these studies was balanced by a presentation of a broad spectrum of cardiology topics: coronary revascularization strategies in stable and unstable coronary syndromes, new pharmacologic therapy and device therapy for heart failure, management strategies for atrial fibrillation, public use of automatic external defibrillators, management strategies for high-risk coronary patients undergoing noncardiac surgery, percutaneous carotid stenting, and percutaneous heart valve implantation.

To provide complete disclosure of any perception of a potential financial conflict of interest, I have now revised my disclosure statement: “Dr. Stone received research grants from Pfizer (not active) and Boston Scientific Corporation (active), served on a now-defunct advisory board for CV Therapeutics, and has served on an advisory board for Pfizer (not active). He has received honoraria from Pfizer for several speaking engagements.”

Peter H. Stone, MD
Brigham and Women’s Hospital
Boston, MA 02115

References
Letters

Potential Financial Conflicts of Interest: Honoraria: P.H. Stone (Pfizer Inc.); Grants received: P.H. Stone (Pfizer Inc. [inactive], Boston Scientific); Advisory boards: P.H. Stone (Pfizer Inc. [inactive], CV Therapeutics [inactive]).

References

Clinical Observations

Regression of Cutaneous and Gastrointestinal Telangiectasia with Sirolimus and Aspirin in a Patient with Hereditary Hemorrhagic Telangiectasia

TO THE EDITOR: Background: Angiodysplastic lesions, including telangiectases and arteriovenous malformations, may affect the organs of many patients with hereditary hemorrhagic telangiectasia (HHT). Abnormalities in transforming growth factor-β signaling and increased production of vascular endothelial growth factor (VEGF) are thought to be responsible for HHT (1). Mucosal hemorrhage from nasopharyngeal and gastrointestinal angiodysplasia is common and is often resistant to conventional treatment. Hepatic arteriovenous malformations may cause arteriovenous shunting within the liver, ischemic hepatobiliary damage, and high-output cardiac failure (2). Liver transplantation may correct the liver complications and heart failure and may also cause regression of cutaneous arteriovenous malformations (spider nevi), probably through correction of estrogen metabolism. Transplantation is not known to induce regression of angiodysplasia elsewhere in the body or to reduce mucosal hemorrhage.

Case Report: A 53-year-old woman whose mother and 2 sisters have HHT was evaluated for jaundice, cachexia, and ascites. The patient had high-output cardiac failure from HHT with hepatic arteriovenous malformations. Over the previous 6 years she received multiple blood transfusions for occult gastrointestinal hemorrhage but remained consistently anemic (hemoglobin level of 80 g/L). Telangiectases were visible on her fingers, chest, lips, tongue, pharynx, esophagus, stomach, and duodenum. No cerebral arteriovenous malformations were present.

The patient underwent liver transplantation 1 year ago to correct her liver and heart failure. Extensive necrosis and multiple, large arteriovenous malformations were found in the excised native liver. Sirolimus to maintain trough levels of 7 to 10 ng/mL and aspirin (81 mg/d) were included in her immunosuppressive regimen because they are reported to inhibit VEGF (3). Low-dose tacrolimus (trough levels of 2 to 5 ng/mL) and prednisone (5 mg/d for the first 6 months) were also used because combination therapy with sirolimus and tacrolimus at these levels reliably prevents rejection (4).

The patient regained normal health without experiencing rejection of the transplanted liver or thrombosis of hepatic vessels. She had no mucosal bleeding in the year since transplantation and was no longer anemic (hemoglobin level of 110 g/L). Telangiectases disappeared from her skin and buccal mucosa within the first 2 months after transplantation and did not recur. Endoscopies at 1 month and at 1 year showed complete resolution of telangiectases from the upper gastrointestinal tract.

Discussion: Although liver transplantation may cause regression of spider nevi, transplantation alone is not known to induce regression of the angiodysplasia of HHT or to reduce mucosal hemorrhage. This report of telangiectasia regression after liver transplantation for HHT suggests that our immunosuppressive regimen may have contributed to the regression, perhaps through its effects on VEGF levels. Tacrolimus does not inhibit VEGF production (5). A recent report documented the remission of Kaposi sarcoma in 15 kidney transplant recipients who converted from cyclosporine to sirolimus therapy (3). The activity of VEGF may play a role in both Kaposi sarcoma and in angiodysplasia in HHT; the regression of telangiectasia with the use of sirolimus therapy after liver transplantation for HHT is consistent with the hypothesis that sirolimus induces regression of Kaposi sarcoma through its action on VEGF. Although aspirin use is normally avoided in patients with mucosal telangiectasia, we included low-dose aspirin in the immunosuppressive regimen to counter concerns about hepatic artery or portal vein thrombosis with sirolimus. We speculate that aspirin may also have contributed to VEGF inhibition by suppressing cyclooxygenase-2 expression. Of note, mucosal bleeding was not encountered in this case while the patient was taking aspirin, suggesting regression of gastrointestinal telangiectases that lay beyond the range of endoscopic visualization.

Conclusion: No pharmacologic therapy has been described for the angiodysplastic complications of HHT. The regression of gastrointestinal telangiectases reported here suggests a potential role for sirolimus and aspirin in the treatment of complicated HHT.

Vivian C. McAlister, MD
University Hospital
London, Ontario N6A 5A5, Canada

Potential Financial Conflicts of Interest: None disclosed.
References


Correction: Update in Cardiology
In the recent Update in Cardiology (1), the author’s potential financial conflicts of interest should have read as follows: “Dr. Stone received research grants from Pfizer (not active) and Boston Scientific Corporation (active), served on a now-defunct advisory board for CV Therapeutics, and has served on an advisory board for Pfizer (not active). He has received honoraria from Pfizer for several speaking engagements.”

Reference