Pharmacoeconomic and Outcomes Analyses in Solid Organ Transplantation

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A number of new immunosuppressive agents have been introduced within the past decade. Each of these agents has produced impressive results in Phase III clinical trials, with acute rejection rates declining from the 40% to 50% range to well under 15% to 25% with newer immunosuppressive combinations. However, with the addition of each agent comes an incremental increase in the cost of therapy, resulting in maintenance regimens that vary in price from $1,700 with azathioprine and prednisone to well over $16,000 per year for some of the newer, more potent combinations. Pharmacoeconomic and outcomes analyses can assist practitioners in identifying optimal strategies for patients when selecting among a number of highly effective but costly agents. Utilization of these techniques, in combination with the evidence-based medical literature, allows healthcare decision makers to make both scientifically and economically sound decisions. The intent of this article is to provide a review of the current pharmacoeconomics literature for transplantation.

Introduction

Over the past decade, progress in the field of transplantation has been accompanied by an increased emphasis on controlling the overall costs associated with it. The average billed charges for the various transplantation procedures in 1999 were $111,400 for kidney, $303,300 for heart, and $244,600 for liver (Table 1).[1-2] Discounted contract reimbursement and Medicare/Medicaid reimbursement typically run much less for any given procedure. Managed care organizations have also implemented the use of contracts based on capitated or global payments inclusive of the transplant hospitalization, physician fees, certain periods of follow-up care (first 90 days to 1 year), and in some cases, also include consultant fees. These types of reimbursement strategies have placed an increased burden on transplant centers to share the risk and has forced them to evaluate both the cost and the effectiveness of various treatment regimens and procedures. Patients also feel the increased pressures of healthcare reform with higher copays, limited lifetime maximums on insurance coverage, and insurers dictating where patients may have their transplants performed (i.e., "centers of excellence"). Costly maintenance immunosuppressive regimens may "spend down" the allocated resources more quickly for a given patient, but this apparent disadvantage must be weighed against the cost of expensive complications, including the possible return to dialysis or need for retransplantation.

To complicate the financial issues further, a number of new immunosuppressive agents have been introduced during the past decade. Many of the multicenter trials have reported impressive results, with acute rejection rates declining from the 40% to 50% range, with cyclosporine and prednisone, with or without azathioprine, to well under 15% to 25% with the newer 3 or 4 drug combination cocktails.[3-9] However, the addition of each agent is associated with an incremental increase in the overall cost of immunosuppressive therapy.[10] Maintenance

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TABLE 1 | CHARGES FOR ORGAN ACQUISITION AND TRANSPLANT PROCEDURES (IN DOLLARS)

	1999 Mean Local Standard Acquisition Charges by OPOs*	Estimated U.S. Average Billed Charges for Transplantation (as of July 1, 1999 ending 1 year after transplant)**							
	Acquisition	Eval	Candidacy	Proc	Hosp	MD	F/U	Immuno	Total
Kidney	16,734	10,000	0	20,500	39,200	8,100	20,000	13,600	111,400
Kidney/Pancreas	-	10,000	0	28,700	56,800	7,900	20,000	14,900	138,300
Liver	17,321	15,000	8,900	25,100	107,600	30,300	45,000	12,700	244,600
Heart	21,908	15,000	8,900	23,700	181,000	23,300	40,000	11,400	303,300
Heart/Lung	21,908	15,000	8,900	22,400	174,900	27,700	40,000	12,300	301,200
Lung	16,977	15,000	8,900	22,400	145,800	12,900	40,000	12,700	257,700
Double Lung	20,195	-	-	-	-	-	-	-	-
Pancreas	16,502	10,000	0	17,900	64,400	7,900	7,500	6,000	113,700
Small Intestine	15,288	-	-	-	-	-	-	-	-

*1999 AOPO Annual Report; **Milliman and Robertson's 1999 report.

TABLE 2 | TYPICAL IMMUNOSUPPRESSIVE REGIMEN COST (AVERAGE WHOLESALE PRICE)

Neoral Cyclosporine (microemulsion) 4.25 mg/kg per day	Sandimmune Cyclosporine 5 mg/kg per day	Mycophenolate Mofetil 1 g every 12 h	Azathiprine 2.5 mg/kg per day	Tacrolimus 0.10 mg/kg per day	Sirolimus 4 mg/day	Prednisone 0.15 mg/kg per day	Annual Costs (AWP)
X		X				X	13,100-13,400
X			X			X	8,400-8,600
X						X	6,100-6,700
	X	X				X	15,100-15,400
	X		X			X	8,600-8,700
	X			X		X	8,600
						X	7,300-8,000
			X			X	1,700-1,900
		X		X		X	13,800-14,800
X					X	X	14,900
				X	X	X	15,500-16,200
		X			X	X	14,700-15,000

regimens vary in price from $1,700 with azathioprine and prednisone to more than $16,000 per year for some of the more potent regimens (Table 2). When reviewing the various multicenter clinical trials, it is apparent that similar reductions in the incidence of acute rejection can be achieved with different regimens. The following question is then called for: Is it possible to achieve the same outcome at a lower cost or a better outcome at the same cost? Certainly, drug therapy for transplantation is expensive; however, this is overshadowed by the costs associated with treating the consequences of failed immunosuppressive therapy. Even though there is a wide variation in reported costs associated with major complications following solid organ transplantation, it is well recognized that the loss of a kidney graft and the return to dialysis and/or the transplant waiting list is neither cost-effective nor beneficial to the patient's quality of life.[11-13]

In the early days of economic analyses, a common, albeit shortsighted, approach was to look only at the actual cost of the given medications, assume outcomes were equivalent, and then use the cheapest product. If that practice were in use today, immunosuppressive regimens consisting of azathioprine and prednisone might still be the mainstay of

TABLE 3 | TYPES OF PHARMACOECONOMIC ANALYSES

ECONOMIC EVALUATIONS	HUMANISTIC EVALUATIONS
Cost of illness	Quality of life
Cost-minimization	Quality-adjusted-life-years
Cost-identification	Patient preferences
Cost-effectiveness	Patient satisfaction
Cost-utility	
Cost-benefit	

therapy. Fortunately, the focus has gradually shifted from using the acquisition cost of the agents to evaluating the overall benefits derived from the therapy. Short-term benefits of the various immunosuppressive regimens are typically measured in terms of avoidance of acute rejection and adverse effects. Ideally, economic comparisons should consider not only these short-term resource savings but also potential long-term benefits, such as improved patient and graft survival, as well as improvements in health-related quality of life. It is important to recognize that the more successful the immunosuppressive regimen is in extending both patient and graft survival, the more cost-effective it will be. Improved long-term outcomes will ultimately benefit society in several ways, including the following:

1. reducing the number of retransplant procedures, allowing the existing organ supply to be used for first-time transplants;
2. reducing the time spent on dialysis and the waiting list; and
3. improving the overall efficiency of the transplantation system.

Types of Pharmacoeconomic Analyses

Pharmacoeconomics is typically considered a subset of outcomes research that deals specifically with pharmaceutical interventions. The therapy can be compared with other drugs, invasive and noninvasive therapy, or even watchful waiting. Pharmacoeconomic analyses can be divided into 2 categories: economic evaluations and humanistic evaluations (Table 3). These studies can be viewed from a number of perspectives, including that of society, the payer, the patient, the provider, or the producer. Specific methods for performing these studies are reviewed elsewhere.[14-16]

Pharmacoeconomic studies attempt to examine total resource consumption, or all costs associated with monitoring a given therapy, including the acquisition cost of the drugs, the cost of providing follow-up services, the cost of side effects, and any other costs such as concomitant medications. Utilization of charge data is often misleading because of cost-shifting that may occur in an institution.[17] Costs can be defined further as either direct (e.g., pharmacy products and services), indirect (e.g., lost productivity), those based on clinical outcomes (e.g., reductions in symptoms), or those based on humanistic outcomes (e.g., QOL). However, costs need to also be viewed relative to the potential savings associated with a diminution in either disease progression or new disease onset, and in light of any complications, which might arise with a standard treatment protocol.

Costs can be divided temporally, into those that occur either in a pretransplant environment (e.g., evaluation and managing the patient's chronic disease), those that occur during the actual transplant itself (e.g., hospitalization-related costs), or those that occur subsequently (e.g., immunosuppressants, rejection therapy 1 year posttransplant, etc.). Clinical outcomes specific to transplant, which need to be accounted for in cost-consequence modeling, include the clinical disease features of rejection, infection, and chronic rejection. Also to be considered are adverse events such as nephrotoxicity, hypertension, hyperlipidemia, and steroid-related complications, and the need for retransplantation along with the attendant possible consequence of mortality. Some of the pertinent variables in cost-consequence modeling for transplantation are described in Table 4. Most of the existing pharmacoeconomic analyses have limited their focus to 1 or 2 of the major drivers of the transplant process (re-

TABLE 4 | VARIABLES IN COST-CONSEQUENCE MODELING

DIRECT MEDICAL COSTS	INDIRECT MEDICAL COSTS	CLINICAL OUTCOMES	HUMANISTIC OUTCOMES
Drug therapy	Noncompliance	Clinical disease features	Functional status
Physician visits	Work days missed	• rejection	Quality of Life
Ancillary services	Family assistance	• infection	Satisfaction
• drug assays	Equipment/maintenance	• chronic rejection	
• nephrotoxicity	Transportation costs	Diagnoses and cures	
Hospitalizations/readmissions/LOS		Adverse effects	
		• nephrotoxicity	
		• hypertension	
		• hyperlipidemia	
		• steroid-related complications	
		• others	
		Retransplantation	
		Mortality	

jection and readmissions during the 1st year) and rarely provide a comprehensive analysis of all aspects listed in this table.

Exclusion of the procedure costs, organ procurement fees, or even initial hospitalization may be appropriate, assuming that the use of a given agent will have little impact on certain factors. Others have highlighted the importance of focusing on the immunologically relevant variables most likely to be affected by a regimen or a given procedure and would exclude those aspects unrelated to transplantation (e.g., hospitalization for a motor vehicle accident is unlikely to be related to immunosuppressive regimen but could dramatically increase length of stay or charge/readmission for a given patient).[17]

Humanistic Evaluations

Economic advantages have been well documented for renal transplantation as compared with dialysis and other healthcare interventions.[1-13,18-20] Health-related quality-of-life (HR-QOL) benefits have been described for various types of organ transplantation.[21] Shield et al. showed that patients who were receiving dialysis for end-stage renal dysfunction had a significant improvement in HR-QOL following kidney transplantation. This study also showed a lower perceived QOL in patients who experienced an acute rejection episode.[22]

To date, very few studies have compared humanistic outcomes of the various immunosuppressive regimens, but as additional agents become available this will become more relevant.

Application of Pharmacoeconomic Methods

Resource Utilization Methods

There are 2 primary methods for collecting data to be used in the economic evaluations of drugs. One way is to collect all the healthcare resources used for any given outcome. Clinical trials are often used as a way to collect major items of resource utilization such as hospitalizations and in-patient resources (drugs, lab tests, etc.). Some studies have attempted to collect actual financial data from each participating center; however, this method is limited by the interinstitution variability of charges/procedure or medication.[23] A better method is to collect actual resource utilization data and then apply standard costs for the various items (i.e., Medicare reimbursement rates, etc.). This eliminates the variability in charges that exists from institution to institution and also the challenge posed by accurately collecting financial data from multiple centers. This method also allows for standardization of charges, as if all of the procedures were performed in one center.

Advantages of piggybacking these studies onto existing trials are that a large number of patients are randomized to the various treatments, the study has been powered to determine whether a statistically significant difference exists in predetermined endpoints, and the majority of the data are already being collected. If designed correctly, the financial or resource use data can be collected in a prospective manner.

The major limitation of piggybacking pharmacoeconomic and outcomes research onto Phase III

multicenter trials (MCT) is the fact that the studies are conducted under highly controlled conditions (i.e., best-case scenario) designed to measure safety and efficacy of a regimen in ideal patients. High-risk patients who typically require more frequent monitoring and dosage adjustments are usually excluded during the screening process. These types of analyses would be better termed cost-efficacy, rather than cost-effectiveness analyses. It is not until the drug is used in the real-world setting that one can truly evaluate its effectiveness or cost-effectiveness. Additionally, the Phase III study has a stringent protocol for monitoring the drug therapy, and once practitioners learn how to use the drug, the monitoring frequency may be different than in the initial phase of the study. This latter factor makes it very challenging because pharmacoeconomic analysis is based on comparing a new medication to one with which practitioners have far more experience. A pharmacoeconomic analysis performed on a Phase III MCT may find there is no additional cost-benefit with the new agent, but it is important to remember the learning curve effect may have an impact on subsequent costs. Another limitation is that the actual cost of the study drug and its monitoring is not known during a Phase III MCT, and in some trials this differential can be sufficient to sway the economic analysis in one direction or the other.

Comparisons of drug regimens, both for effectiveness and economics, should be conducted in large, randomized, prospective multicenter trials, and ideally performed 3 to 5 years after the drug has been approved, when everyone has experience using the new medication. Realistically, it is unlikely that the pharmaceutical industry would fund a study of such magnitude once the drug is approved and in widespread use.

Pharmacoeconomic Modeling Techniques

As described above, prospective pharmacoeconomic studies can be very complicated and take years to complete. Administrators typically want to know what impact a new medication, device, or procedure will have on their institution's financial status in real time rather than waiting for actual results. Therefore, alternative strategies using statistical techniques are frequently used to predict future implications based on existing data and certain assumptions. Pharmacoeconomic studies commonly employ one or more of the following techniques to answer economic questions in a timely manner: modeling, decision analysis, or meta-analysis.

Modeling data have become a popular way of applying pharmacoeconomic analyses to various sources of data available within and outside healthcare organizations.[24] Sources of data include medical records, financial and administrative databases, expert panels, randomized clinical trials, medical claims databases (e.g., Blue Cross and Blue Shield), government or other databases (e.g., Medicare, Medicaid, USRDS, UNOS), and private consultants. These types of studies typically use existing clinical and epidemiologic data to project the effect of a clinical, policy, or medication decision on a patient, population, or organization.

Advantages of modeling include that it is a relatively inexpensive and timely means of obtaining pharmacoeconomic data (i.e., utilizes existing data rather than repeating the study or collecting new data). Modeling can also serve as a bridge between efficacy data and effectiveness data, allowing one to populate the model with local or internal data rather than only using data from Phase III trials.

Modeling studies are also inherently disadvantageous, largely because they are approximations that are only as good as the assumptions made and the sensitivity of the model. Modeling also has the potential to introduce bias into its findings. It has been suggested that models can be designed to support any results desired by a researcher, sponsor, or decision maker. If a stakeholder sponsors the study, a degree of skepticism exists with any conclusions. It is also unlikely that a negative pharmacoeconomics study will be published if it reflects poorly on the sponsor's product. Another limitation of modeling involves the quality of data incorporated into the model. The quality can vary greatly depending on the source and the rigor under which the data were collected. Finally, because of a lack of familiarity with modeling techniques, practitioners may question the value of data derived this way.

The easiest way to model one's own data is to adapt an existing model to one's specific institution by substituting outcomes data and institutional costs. This is not always possible because some of the

models published in the literature do not provide adequate detail to allow you to perform your own calculations, nor do they always share the same key variables for your setting. Certainly, institutions with a heavy managed-care influence may have different priorities than those with less capitation.

Clinical Decision Analysis

Decision analysis is a modeling technique used under conditions of uncertainty. It quantitatively describes a problem in terms of multiple possible courses of action, probabilities that certain events and outcomes will occur, and the value of the expected outcomes resulting from those different courses of action. By combining the probabilities that events will occur with the value of each possible outcome, decision analysis determines which option to select to maximize the outcome of a given decision. A commonly used component of decision analysis is called the decision tree that incorporates the various outcomes. A variety of software packages exist to aid the clinician in performing decision analyses.

The main advantage of decision analysis is that it forces the user to structure a decision as well as identify the consequences of the possible decision outcomes. It is quantitative in that it forces the user to assign probability estimates and outcome valuations to identify the best outcome. Decision trees allow a therapeutic management problem to be separated into discrete manageable steps and work best for problems involving events or interventions that occur once over a short period of time. Furthermore, a treatment decision model can be based on the relative nature and degree of costs incurred under different treatment scenarios. Unfortunately, the majority of treatment decisions made today are not based on such models, largely because of the lack of suitable comparative published studies and because of the natural bias toward the selection of studies with positive findings for publication.

The main disadvantage of decision trees is that they can become very complex (i.e., multiple sequential branches) when trying to deal with events that occur repeatedly (e.g., acute rejection and infection) or over a prolonged period of time (e.g., chronic rejection). In these situations, it is better to use an alternative method, such as Markov modeling, which allows a patient to move from one condition to another.

Markov Modeling

Depending on the circumstances, a simple decision tree may not be adequate to address complex issues that can be characterized by the recurrence of various conditions. Conventional decision trees describe the various ways a group of patients in one state of health may end up in other states over a fixed period.[24] Markov models, alternatively, focus on transitions among a number of possible health states (e.g., healthy, diseased, diseased with complication, and dead) during a series of time cycles.[25-26] The general idea behind Markov modeling is that a patient can be in one state of health at any given time and that the patient's health status can change from that state to another and in some situations back again, depending on a set of transition-related probabilities.[24-26] Potential transplant "states," in which the patient might be categorized, include well, rejection, CMV infection, other infection, chronic rejection, malignancy, renal failure, and death. Markov modeling is the most commonly used method, but other multistate models are reviewed elsewhere.[27]

Advantages of Markov modeling include its utility for more accurately reflecting the various states in the clinical course of transplant patients. It can also be used to predict the impact of a change in immunosuppressive therapy on the expected survival and frequency of other events (e.g., what impact does a 50% reduction in rejection that results in a 50% increase in CMV have on survival and on long-term costs?). A limitation of this method includes using data from clinical trials, which may or may not provide information regarding new immunosuppressive regimens. For instance, it would be difficult to model the efficacy of different CMV prophylactic regimens in a sirolimus regimen if there are no data reporting the efficacy of a sirolimus-based regimen. One could make the assumption that the antiviral regimens are equally efficacious as in azathioprine or mycophenolate mofetil regimens, but this assumption would completely influence the outcome of the model. Similarly, if controlled trials are lacking for regimens currently in use, it is not possible to populate a

model with such data unless it is available in some other setting. Another limitation of the Markov model is the assumption that clinical events or states are mutually exclusive when, in fact, it is possible for a patient to have a rejection episode and a CMV infection at the same time or an acute rejection episode superimposed on chronic rejection. The model is only as good as the assumptions upon which it is based.

Markov modeling has primarily been used in transplantation for predicting trends such as number of patients requiring renal replacement therapy and transplantation in Denmark,[28] Canada,[29] and Australia;[30] distribution of donor hearts to maximize recipient survival;[31] progression of allograft vasculopathy after heart transplantation;[32-33] and analyzing the cost of main clinical events after cardiac transplantation.[34]

Cost of Transplant-Related Complications

Acute Rejection

The cost of maintenance immunosuppression is high (Table 2). However, the cost of treating an acute rejection episode is also expensive if it does not respond to pulse steroid therapy. The cost to treat an episode of acute rejection is approximately $3,300 with a course of steroids and $14,500 with a course of antilymphocyte therapy, but may be even higher depending on the number of courses and duration of therapy needed to reverse the process.[18,35]

CMV Infection

CMV infection is well recognized for increasing length of stay and hospitalization charges following both kidney and liver transplantation.[36-38] A number of economic studies have supported the use of ganciclovir[38-40] in organ transplant patients, whereas valacyclovir was studied in another.[41] Two of the studies supported antiviral prophylaxis only in the highest risk groups.[39,41] The economic results from the valacyclovir study, using the French healthcare system perspective, were difficult to apply to U.S. centers since the length of stay was much longer than currently reported in this country.[41]

Das constructed a Markov model to compare the cost-effectiveness of different prophylactic strategies for CMV in a hypothetical cohort of 1000 liver transplant patients.[42] Seven possible posttransplantation states of health were included in the analysis: healthy, those undergoing acute rejection, those with chronic rejection, patients with CMV infection but no disease, patients with CMV disease, those with CMV disease complicated by opportunistic infections, and the 7th state was death related or unrelated to CMV. The model was limited to the 1st year after liver transplantation to simulate the usual period of CMV-related morbidity and mortality and because of the lack of literature using CMV prophylaxis beyond this time period. Antiviral strategies included providing prophylaxis to all patients or to high-risk patients only (D+R-, steroid-resistant rejection, OKT3) and consisted of 5 different regimens (IV ganciclovir x 100 days, oral ganciclovir x 100 days, CMV immune globulin up to 16 weeks, acyclovir x 6 months, acyclovir x 3 months). In the initial analysis, all patients received some type of prophylaxis, with IV ganciclovir and oral ganciclovir identified as being the 2 best strategies. These 2 agents were then used in the 2nd stage of analysis to determine whether universal prophylaxis or selective administration to high-risk patients was preferable. Based on the incremental cost-effectiveness ratio, universal oral ganciclovir was the most favored strategy.

This outcome is not surprising considering the most effective strategies were the 2 different ganciclovir regimens (IV vs. PO); however, the model is limited in that it assumed IV ganciclovir would be administered for the full 3 months, which is more costly as compared with oral therapy for 3 months. Another limitation of the study is that some currently used combinations of CMV prophylactic agents (e.g., IV ganciclovir followed by PO ganciclovir, CMV-Ig in combination with ganciclovir) were not included. Similarly, the analysis of universal versus selective prophylaxis only compared these strategies against using no prophylaxis whatsoever, rather than against other contemporary regimens such as targeted preemptive therapy.

Steroid-Related Complications

Veenstra et al. used Markov modeling to predict the incidence and long-term cost of steroid-related side effects after renal transplantation.[43] Data on the incidence of steroid-related complications (e.g.,

hypertension, posttransplant diabetes, peripheral bone fractures, avascular necrosis, cataracts) were obtained from the transplant literature and were limited to studies using cyclosporine-based immunosuppression. If data were not available in the transplant literature, other sources from the medical literature were used. A 10-year time frame was selected for capturing the costs of steroid-related side effects as it would reflect the average graft survival of a kidney transplant recipient. The most costly side effects were hypertension and posttransplant diabetes. The cost of treating steroid-related side effects over 10 years ranged from $2,500 to $7,500 per patient or $265,900 for the 50-patient cohort. Limitations of this analysis include the fact that not all steroid-related side effects were included such as lipid disorders and cardiovascular complications, hip fractures, glycemic control in patients with preexisting diabetes and diabetes-related complications, and stunted growth, nor were changes in quality of life related to steroids considered. These additional adverse effects may have increased the overall cost per patient.

This study highlights the importance of considering the costs and long-term consequences of immunosuppressant-related side effects. Certainly, as the economics of the various new immunosuppressive regimens are evaluated, it will be important to factor in the cost of using steroids when making decisions between equally effective but possibly steroid-free regimens.

Pharmacoeconomic Evaluations of Current Immunosuppressive Regimens

Economic studies evaluating immunosuppressive regimens have used the various procedures described above, although most have focused on the short-term impact of immunosuppressive therapies and limited their analysis to hospitalization costs and/or readmissions during the 1st year posttransplant. Some have included out-patient data, but on a limited basis.

Cyclosporine (Sandimmune, Neoral)

The introduction of cyclosporine dramatically increased the cost of maintenance immunosuppression for transplant patients. However, previous studies have shown that the cost of adding cyclosporine to the regimen was offset by decreased readmissions for treatment of acute rejection during the 1st year after transplantation, making transplantation more cost-effective than dialysis.[12,44-46]

More recently, a number of economic analyses based on resource utilization have been conducted comparing the 2 cyclosporine formulations. Most were simple cost analyses that compared the direct medical costs of immunosuppressive therapy during the short term (e.g., 12 weeks to 1 year posttransplant) after renal or hepatic transplantation. Two preliminary economic studies in Canada performed on the data from a stable conversion study and a de novo trial compared Neoral with the older cyclosporine (Sandimmune).[47,48] These studies did not produce any statistically significant cost differences as resource utilization was similar in the 2 treatment groups, although there was a trend in favor of Neoral. Both studies enrolled a small number of patients, 30 and 41, respectively, and the duration was only 12 weeks. Another study in Europe enrolled 68 patients into a de novo trial, and these patients were followed for 12 months. From a societal perspective, potential savings of 27% from the use of Neoral was identified when compared with Sandimmune.[49] In 3 other economic analyses, there was an overall cost advantage for Neoral in de novo livers of about 8% to 10% at 4 months,[50] an advantage for Neoral versus IV in liver patients with respect to costs associated with acute rejection,[51] and a cost savings from dosage reduction in a conversion trial at 6 months posttransplant.[52] A limitation of the above studies was that the studies were not primarily designed to test economic hypotheses. Most were not powered to detect a statistically significant difference in clinical outcome, and thus it is no surprise there were not statistically significant cost differences other than the savings produced by the differential pricing of Neoral versus Sandimmune.

Lewis et al. used Markov modeling to evaluate the cost-effectiveness of de novo Sandimmune cyclosporine versus the modified solution Neoral.[53] The 2 Neoral cohorts were composed of 35 primary CAD renal transplant recipients participating in U.S. trial OLM 103 (Neoral-US) and an aggregate of 77 patients studied in European trials OLM 103, OLM 104, and OLM 105 (Neoral-EUR). Each tri-

al was a prospective, parallel group, randomized, double-blind comparative study of de novo Sandimmune (SIM) versus Neoral conducted during 1992 and 1993. Follow-up in each of the trial cohorts was limited to 12 weeks at the time of data analysis. The Sandimmune-treated patients consisted of the current controls participating in the U.S. de novo Neoral trial (SIM-US, $n = 32$) and a cohort of 4737 Sandimmune-treated, 1st-CAD transplant recipients selected from the U.S. Health Care Financing Administration (HCFA) databases (SIM-HCFA).

A Markov decision analytic model was constructed for each study cohort by assigning one of the following 4 health states to each patient: no previous rejection, one or more previous rejection episode(s), return to permanent dialysis because of graft failure, and death.[53]

Patients remained in the same health state or were transmitted to another health state at the end of arbitrarily selected, discrete-time intervals referred to as Markov cycles. The present model was run for 6 cycles, each of 15 days duration, to encompass an observation period of 3 months. Probabilities of rejection, graft loss due to rejection, graft loss due to other causes, and death were calculated for each 15-day Markov cycle. The cumulative probabilities of these events were then calculated and, together with itemized cost data, used to calculate the costs per functioning graft and per rejection-free clinical course for the first 3 months following transplantation.

Because the rejection rates within the various Neoral and Sandimmune cohorts varied so greatly and overlapped (32% to 45% and 26% to 61%, respectively), the data did not demonstrate a conclusive difference with respect to cost-effectiveness. The major limitations of the study were the small sample sizes in each of the de novo clinical trials, protocol-driven patient management and resource utilization in the clinical trial patients, and differences in European versus U.S. practice patterns that were not characterized in the de novo study databases. Another major limitation of the study was that the HCFA database was unable to distinguish between an antibody-treated versus corticosteroid-treated rejection episode, and a mean cost for all rejection episodes was calculated. Certainly the use of the actual cost for either polyclonal or monoclonal rejection therapy might have swayed the financial analysis.

Tacrolimus

Several studies have been conducted evaluating the short-term data comparing tacrolimus and cyclosporine based on studies in Europe and the United States.[23,54-60] The majority of the studies focused on direct medical costs during the short term (e.g., 1st year) after renal or hepatic transplantation and were associated with immunosuppressive therapy and readmissions for acute rejection. In some of the studies, an overall cost advantage for tacrolimus of about 10% to 20% was reported,[23,57,61] whereas others reported specific cost advantages (e.g., costs associated with acute rejection,[23,60] immunosuppressive regimen,[54,57,59] and subsequent rehospitalizations[55,57,58]). Most of the cost benefits of tacrolimus over cyclosporine were the result of lower rates of acute rejection reported with tacrolimus maintenance therapy.

It is always important to evaluate all of the data presented within an economic study. A good example of this is in a recent U.K. study that used a retrospective design to analyze resources used in the management of adult cadaveric renal transplant patients with Neoral or tacrolimus as primary immunosuppression.[56] Eighty-nine patients with at least 6 months of follow-up were included in a cost analysis of hospital expenditures for that time period. The authors concluded that there were similar overall direct medical costs, with mean costs being 13,200 pounds for Neoral and 12,982 for tacrolimus patients; however, key factors including death, graft loss, and return to dialysis, which were higher in the Neoral group, were not included in the financial analysis.

Short-term and long-term benefits for tacrolimus were reported in a study by Gjertson and colleagues reviewing the data on 38,057 first cadaveric kidney recipients in the UNOS Kidney Transplant Registry from 1988 through 1994. One-year graft survival rates of 91.1% ± 1.3% versus 86.6% ± 0.2% were reported for tacrolimus versus cyclosporine, respectively. They estimated a significantly longer graft half-life of 14.5 years for the tacrolimus and 8.8 years for the cyclosporine

group.[62] If these figures are accurate, the implication is that the cyclosporine group will incur the extra cost of returning to dialysis or need for retransplantation 5 years sooner than the tacrolimus patients. Another interesting finding in this analysis was that 60% of the tacrolimus patients were reported to be steroid free by 1 year as compared with only 15% of the cyclosporine-treated patients. The graft half-life in the tacrolimus patients successfully withdrawn from steroids was 26 ± 10 years. The primary limitation of this study was that only 24 (11%) of the centers contributed the tacrolimus patients. It is difficult to discern whether the improvement in graft survival is a reflection of the primary immunosuppressant or whether these patients, the majority of whom were steroid free, represent an immunologically privileged population, or whether steroids contributed to the decreased graft half-life seen with the other patients.

Mycophenolate Mofetil

An economic analysis based on the mycophenolate mofetil (MMF) multicenter clinical trial evaluated the costs of quadruple therapy involving induction, cyclosporine, corticosteroids, and MMF or azathioprine in the 1st year after transplantation.[63] Treated acute rejection rates, graft failure rates, and medical care utilization data obtained directly from the U.S. trial were used as inputs to the economic analysis. Additional data were obtained from American Hospital Association annual reports (hospital per diem cost estimates), Medicare End-Stage Renal Disease program reports (annual dialysis and functioning graft expenditures), and literature-base patient preference (utility) estimates. Data from a U.S. quadruple therapy induction trial demonstrated a statistically and clinically significant reduction in the incidence of biopsy-proven acute rejection or treatment failure at 6 months (47.6% in the control group vs. 31.1% in the MMF 2-g treatment group [P = 0.0015]).[6] The clinical results showed a much lower incidence of rejection, better graft survival, and no difference in the incidence of opportunistic infections with MMF therapy. Even though MMF was more expensive than azathioprine, the cost of MMF was offset by the lower 1st-year treatment costs for rejection, dialysis, and graft failure. MMF was deemed to be more cost-effective from a societal perspective than azathioprine, and even in the worst-case scenario, with sensitivity analysis applied, MMF was cost-neutral at the end of 1 year.

Two other economic analyses with MMF were performed in Canada but provided conflicting data, with one reporting slightly higher costs with MMF therapy[64] and the other finding MMF to be more cost-effective.[65] Limited data are available as both were only reported in abstract form. Three other single-center analyses reported early economic benefits from the health system perspective, primarily related to the decreased incidence of rejection 3 to 6 months posttransplantation and less need for expensive antilymphocyte therapy.[66-69]

Sirolimus

Limited pharmacoeconomic data are available for sirolimus. A recent abstract described an economic analysis using Medicare claims data for the 1st year charges from the recent U.S. sirolimus safety and efficacy trial.[7] The analysis showed lower inpatient and physician/supplier charges ($4600) for the sirolimus 2 mg/day arm as compared with azathioprine; however, the cost of the study drugs was excluded.[70]

Induction Regimens

Much controversy has existed regarding the benefits of induction therapy as the randomized trials have failed to show improved allograft survival. Szczech et al.[71] recently conducted a meta-analysis of these trials, which showed a benefit of induction at 2 years, particularly among presensitized patients, and in the latter population, the patients continued to have a benefit at 5 years.

This controversy also exists for pharmacoeconomic analyses of the various products as conflicting data exist for the comparative studies and reflect the differences that may occur at single centers versus pooled data from multicenter trials.

Shield et al. compared the cost of induction therapy with OKT3 versus no induction therapy with cyclosporine, azathioprine, and prednisone by modeling clinical trial results with financial data from separate sources.[22] Cost estimates were based on results from a 5-center randomized trial com-

paring OKT3 induction with conventional triple drug therapy in 207 patients. Financial data were obtained from the National Cooperative Transplantation Study, the Medicare Provider and Analysis Review database, and other sources. The comparative measures included costs incurred between transplantation and graft failure, the effectiveness of the 2 regimens as defined by length of graft survival, and cost-effectiveness ratios through 5 years of observed follow-up, and modeled beyond 5 years by assuming a graft failure rate of 4% annually. The authors concluded that the initial cost of the OKT3 induction therapy was almost offset by savings assoc- iated with a lower acute rejection rate and a trend for better graft survival. However, depending on which parameter is evaluated, one could conclude that OKT3 is more expensive, less expensive, or cost-neutral. Another single-center study reported favorable results and improved cost-effectiveness with a shorter course of OKT3 therapy, but they did not perform a formal economic analysis.[72]

Schommer et al.[73] performed a retrospective analysis comparing the economics of ATG and OKT3 in a retrospective, multicenter study using charge data obtained from the HCIA "Clinical Pathways Data Base." Five hundred fifty-two patients who had received either OKT3 or ATG were selected from 22 hospitals. The authors concluded that the increased pharmacy charges for ATG were partially offset by reductions in ancillary charges. In a subsequent publication, the authors pointed out the limitations of using secondary databases and that significant variations between hospitals' clinical practices and charging policies made interpretation of the results difficult.[74]

Brennan et al. conducted a retrospective analysis of their single-center experience of 183 patients receiving induction therapy with either ATG or OKT3.[75] There were some demographic differences between the 2 groups as the ATG patients were older, which might have contributed to the lower incidence of rejection, but more extended donors were also used in that group. The 1-year posttransplant rejection was lower for ATG (34% vs. 47%) than for OKT3, and graft survival was better in the ATG group (93% vs. 85%). The overall hospital-related costs for ATG ($39,937 ± $17,014) and OKT3 ($42,850 ± $20,923 for OKT3) were similar.

Schnitzler et al.[76,77] demonstrated cost savings for thymoglobulin as compared with ATG in the treatment of acute rejection. This pharmacoeconomic study was conducted from the perspective of Medicare and performed on the data from 163 patients enrolled in the randomized double-blind 25-center trial evaluating the safety and efficacy of these agents in reversing acute rejection. The study focused on the first 90 days following initiation of rejection therapy and assessed differences in immunosuppression, therapy for refractory rejection, CMV treatment, and return to dialysis, and complications requiring hospitalization were included in the analysis. Thymoglobulin was associated with a significantly lower cost (overall $5277 savings) during the 90 days posttherapy, with a cost difference of $7133 in recipients of cadaveric donors. Savings ranged from $6,581 to $12,509 in other high-risk subpopulations. It is important to note that the cost of both study agents was excluded, as thymoglobulin had not yet been priced and inclusion of this information could change the savings differentials.

Other Methods to Reduce the Cost of Immunosuppressants

Other efforts that have been used to reduce the costly nature of immunosuppressants include the intentional administration of interacting medications (e.g., ketoconazole, diltiazem, itraconazole, erythromycin) or food products (e.g., grapefruit juice).[78-80] These strategies for reducing dosages, necessary to achieve therapeutic concentrations, are dependent on the competitive inhibition of cytochrome P-450IIIA4 enzymes and p-glycoprotein to improve the absorption of agents such as cyclosporine, tacrolimus, and sirolimus. A dosage decrease and cost savings can be achieved by these strategies, but the added monitoring costs need to be considered.

Summary

As more and more immunosuppressive agents are introduced to the market, practitioners need to scrutinize both the reported clinical results and the subsequent economic analyses. A number of so-called pharmacoeconomic studies have been published in the literature, but most are limited by

their narrow focus. The majority of these analyses have shown favorable or at least neutral results. Close attention must be paid to determining whether the results are applicable in the clinical environment or whether the healthcare decision makers need to recalculate the anticipated cost benefits based on their own data. In these situations, modeling techniques can be employed to ensure that product selection is cost-effective. Scientifically sound economic analyses should be performed on a routine basis; however, rather than piggybacking economic analyses onto Phase III clinical trials, these studies should be conducted after practitioners have adequate experience with the new agents. Guidelines for such studies have been published elsewhere.[81]

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