Determining the Real Cost of Keeping Transplant Patients Well: Evaluating Pharmacoeconomic Studies in Transplantation Medicine

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The recent introduction of several new immunosuppressive agents has prompted the need to evaluate not only the comparative efficacy and safety of these agents but also the cost of using the newer regimens. Many of these regimens have produced impressive results, with acute rejection rates declining from the 40% to 50% range with dual therapy (cyclosporine and prednisone) to under 15% to 30% with some of the triple or quadruple regimens.[1-15] The introduction of each new agent, however, brings an incremental increase in the cost of therapy.

Triple drug therapy maintenance regimens vary in price from a low of $6000 with the use of generic agents, cyclosporine, azathioprine, and prednisone, to well over $16000 per year for some of the new, more potent brand name combinations. In 1996, medications were reported to account for 25% of the total cost of care in the first year after transplantation and up to 90% in subsequent years.[16] This proportion may be even greater today.

It is important to recognize that the annual cost of a given regimen can be dwarfed by the cost of complications. Steroid-resistant acute rejection episodes, graft loss, and the subsequent need to return to dialysis or to the transplant waiting list, or—in a worst-case scenario—patient death, are considerations that factor heavily in the selection of optimal regimens based on specific patients' needs. Placing a dollar value on complications such as these makes drug therapy seem like a bargain. A more costly maintenance regimen may be justifiable if one is able to avoid expensive and potentially life-threatening complications.

Obviously, managed care organizations, private insurers, the government, and individual institutions are all interested in containing costs and would welcome well-designed economic analyses that might assist them in making tough decisions regarding costly therapies. Committees at these institutions typically try to reduce costs by limiting access to a number of agents. In most situations, there exists a mandate that if a new drug is to be added to the formulary, then another should be eliminated.

These committees rely heavily on the use of evidence-based medicine to make their decisions. However, many of the decision makers (e.g., formulary committees at hospitals, managed care organizations, pharmacy benefit management groups) are not directly involved in the area of transplantation, and this complicates the process. Committee members may not be familiar with the nuances of transplant multicenter trials (MCTs). Committees unfamiliar with these trials commonly ask, if a new drug does not improve patient or graft survival, then why should it be used? This demonstrates a lack of understanding that many of the MCTs are not adequately powered to detect differences in those endpoints, especially when graft and patient survival rates in excess of 90% are common in the context of kidney transplantation.

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Kathleen Lake, Pharm.D., B.C.P.S.
University of Michigan Health System
Division of Nephrology
3914 Taubman
Box 0364
Ann Arbor, Michigan, USA 48109-0362
Tel.: 734.936.5645
Fax: 734.936.9621
email: kdlake@med.umich.edu

thought process for product selection that is used for the nontransplant patient, regardless of whether the drug is an immunosuppressant, a beta blocker, a calcium channel antagonist, or a quinolone antibiotic. In addition, as we will see, there are issues regarding the way many transplant studies are typically conducted that warrant a closer look if we are to derive maximum value from the work that is being done. The need for valid information provided in a timely manner will be increasingly critical as a number of new drugs are launched. Therefore, the time is right for those in the practice of transplant medicine to decide what kinds of studies are truly helpful, then advocate their development. Otherwise, especially in the face of a plethora of new, and not uniformly useful, data, we risk choosing new protocols that may not be in the best interest of patients.

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Raising the Standards of Transplant Studies: Points to Consider

The recent increase in the number of publications addressing issues related to economics and quality of life in transplantation would give the impression that the need for scientifically sound data is being met by these studies. However, few of these analyses are providing useful information. In fact, most transplant practitioners do not base their drug therapy decisions on them. Many of these so-called economic studies represent the marketing interests of the pharmaceutical industry. From the industry's perspective, there is a perceived value associated with demonstrating the cost-effectiveness of a given drug or regimen, especially when many of the new regimens achieve similar results and are more costly than the older therapies.

In 1999, a group of transplant professionals met to address concerns regarding the quality of this research and created a consensus document on the conduct and reporting of economic and quality-of-life studies.[17] This document is a step in the right direction, but far more work needs to be done to ensure that these guidelines are implemented into clinical studies.

Although some of the recently published economic analyses involve a single center, many economic trials have been performed in conjunction with prospective, randomized MCTs. The value of these studies is limited by the design of the original trial and the fact that they do not necessarily address the specific needs of health care decision makers. It is important to recognize that Phase III trials are intended to evaluate the safety and efficacy of a new drug, ultimately leading to its approval by the FDA. They are not designed to evaluate head-to-head comparisons of the newest therapeutic combinations, which is what practitioners really need.

There are apparent advantages of combining economic studies with existing trials. The trials typically include a large number of patients randomized to the various treatments and have been designed to determine whether statistically significant differences exist in predetermined endpoints. The majority of the data are in the process of being collected. If the trials are designed correctly, it may be assumed that the financial or resource-use data can then be collected for use in other prospective studies.

However, a closer look reveals a number of limitations in combining pharmacoeconomic and outcomes research with Phase III MCTs. These studies are conducted under highly controlled conditions (i.e., best case scenarios) designed to measure the 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 enrollment process. Because of strict inclusion/exclusion criteria, these types of analyses would be better termed "cost-efficacy" rather than "cost-effectiveness" analyses. Only in real-world settings (i.e., Phase IV and beyond) are we able to truly evaluate a drug's effectiveness or cost-effectiveness.

Additionally, the Phase III study has a stringent protocol for monitoring the drug therapy. 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 poses a challenge, because the 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 at first reveal no additional cost-benefit in relation to the new agent; it is important to remember that the "learning curve effect" may have an impact on subsequent costs. Another limi-

tation is that the actual cost of the study drug, and its monitoring, is simply not known during a Phase III MCT. In some trials, this differential can be sufficient to sway the economic analysis in one direction or the other.

It is also important to note that the study design of MCTs has changed over the past decade. Originally, trials enrolled only cadaveric recipients, in part owing to a concern regarding the risk associated with subjecting a lower-risk patient (i.e., recipient of a living related donor kidney) to an experimental drug, and because at that time the majority of patients were recipients of cadaveric organs. As the percentage of living donors has increased nationwide to more than 50% at some centers, the demographics of clinical trials have also changed. The most recent MCTs have included a large number (27% to 39%) of recipients of living donors.[4,12,18] Using recipients of both cadaveric and living donor organs certainly expedites the timely completion of these studies. However, pooling data from cadaveric recipients and the lower-risk living donor recipients can complicate the interpretation of the results. It is likely that the overall incidence of acute rejection would be higher for a given regimen if the MCT enrolled only recipients of cadaveric organs.

Although some of the studies have broken down the results according to donor type (e.g., cadaveric vs. living), one must be cautious when interpreting the results from subgroup analyses, as many of these are not adequately powered to detect a difference.[18,19] The question follows, what do you do with the data if the results are conflicting—for example, the drug's efficacy varies in living donor organs versus cadaveric, Caucasians versus African Americans, males versus females?[12,18] Ideally, we would like to know if these findings are real, and then we could avoid less effective therapies in certain patient subgroups. However, subsequent analyses that attempt to address these questions are rarely designed to answer them.

Primary endpoints have also changed over time. The success of renal transplantation, with patient and graft survival exceeding 90%, has complicated the interpretation of clinical results, as most of the trials are not designed with these expected endpoints. This success has resulted in the need to use alternative endpoints (e.g., acute rejection) or a composite endpoint (e.g., combined incidence of acute rejection, graft loss, and death) to evaluate the safety and efficacy of therapy.

Another criticism of some of the recent clinical trials is that the control arm in the study is not reflective of the current practice. Dual therapy (e.g., cyclosporine and prednisone) is used in many European studies but is not considered the standard of care for most U.S. renal transplant centers. In general, it is assumed that a new drug combination is more effective than cyclosporine and prednisone. However, most practitioners in the United States are more interested in knowing how a new regimen compares to triple therapy, with at least azathioprine, or preferably mycophenolate mofetil in the control arm.

In addition to differences in maintenance immunosuppression, the use of European trials for decision making is also limited by the fact that the racial demographics are much different than those seen in most U.S. trials. The various European trials enroll 0% to 3% African American patients, whereas the U.S. trials usually enroll at least 20% to 25% African American patients. However, some of the recent trials have enrolled up to 50% of the patients as non-Caucasians.[5,8] Results from a Caucasian population are not necessarily generalizable to a racially diverse group of patients.

Time of randomization can represent another confounding factor in many of these trials. Intent-to-treat analyses are considered the gold standard for evaluation; yet, when randomized patients never receive a dose of study medication because they are unable to take oral medications, or they die prior to treatment, it complicates the interpretation of the results.[20] More recently, trials have allowed randomization of patients up to some time interval following transplantation, but this can complicate the comparison of different regimens when one study randomizes prior to transplantation, and another randomizes 48 h later when the patient has good graft function.[12] In the latter situation, patients with delayed graft function would be excluded, and the outcomes are likely to appear to be more favorable than if these patients had been included.

When reviewing the various trials (see Table 1), it is apparent that similar reductions in the incidence

Table 1 | **Comparative Results of the Various Treatment Arms in Recent Clinical Trials**

Study	N	CAD (%)	AA/NC (%)	Retx (%)	Therapy	BPAR (%)	SRR (%)	CMV (%)
Europe Simulect[21]	186	100	0.5/3.7	0	CsA-Pred	54.8	23.1*	26.9
US Simulect[18]	173	71	34.0/39	0	CsA-Pred	49.1	29.9	9.2
Europe MMF[2]	166	100	N/A	9	CsA-Pred	46.4	18.7	2.4
Europe Zenapax[22]	130	100	2.0	0	CsA-Pred	42.0	35.0	25
Global SRL[13]	130	76	N/A	N/A	CsA-Pred	42.0	9.0	N/A
US Tacro vs. CsA[5]	207	100	23.2/40	13.6	CsA-AZA-Pred-Ind	46.4	25.1	N/A
Europe Tacro[6]	145	100	N/A	10	CsA-AZA-Pred	45.7	21.6	16.6
Europe SRL[14]	41	100	0/2	0	SRL-AZA-Pred	41.0	17.0	14
Europe SRL[14]	42	100	2/12	0	CsA-AZA-Pred	38.0	12.0	12
US MMF[1]	166	100	24.1/38	0	CsA-AZA-Pred + ATG	38.0*	20.1	6.1
US Zenapax[9]	134	100	20/40	0	CsA-AZA-Pred	35.0	14.0	10
US SRL[24]	161	74	25/43	0	CsA-AZA-Pred	31.1	12.4	5.6
Europe Simulect[21]	190	100	1.6/5.8	0	SIM+CsA-Pred	37.9	10.0*	20.5
US Simulect[18]	173	69	27.0/32	0	SIM+CsA-Pred	35.3	20.2	6.9
Miller Tacro MMF 2 dosages[23]	59	100	18.6/44.1	8.5	Tacro- MMF 1g - Pred + Ind 62.7%	32.2	11.9	6.8
Miller Tacro MMF 2 dosages[23]	59	100	15.3/50.8	8.5	Tacro-AZA-Pred +Ind 64.4%	32.2	8.5	5.1
US Tacro vs. CsA[5]	205	100	27.3/44.4	13.2	Tacro-AZA-Pred-IND	30.7	10.7	N/A
Europe Zenapax[22]	140	100	N/A	0	ZEN +CsA-Pred	28.0	28.0	18
Kreis SRL/MMF vs. CsA/MMF[15]	40	100	3/5	0	SRL-MMF-Pred	27.5	N/A	5.0
Thymoglobulin vs. ATG[25]	24	79	25.0/29	4	CsA, AZA-Pred +ATG	25.0	N/A	33.3
Global SRL[13]	227	77	N/A	N/A	CsA-SRL 2 mg-Pred	25.0	4.0	N/A
Europe Tacro[6]	303	100	N/A	9.6	Tacro-AZA-Pred	25.9	11.3	13.5
US Zenapax[1]	126	100	19/33	0	ZEN + CsA-AZA-Pred	22.0	8.0	12
US SRL[24]	284	63	22/44	N/A	CsA-SRL 2mg-Pred	21.8	5.6	3.2
Johnson Tacro/MMF vs. AZA[7]	75	100	22.7/33.3	0	CsA-MMF-Pred+ Ind 28%	20.0	10.7	2.7
US MMF[1]	167	100	26.3/39.5	0	CsA-MMF 2 g-Pred + ATG	19.8*	10.3	9.1
Kreis SRL/MMF vs. CsA/MMF[15]	38	100	0/8	0	CsA-MMF-Pred	18.4	N/A	21.0
US MMF[1]	166	100	19.9/28.9	0	CsA-MMF 3g –Pred + ATG	17.5*	5.4	10.8
Europe MMF[2]	165	100	N/A	10.0	CsA-MMF 2 g -Pred	17.0	3	15.8
Johnson Tacro/ MMF vs. AZA[7]	76	100	13.2/28.9	0	Tacro-AZA-Pred + Ind 32.9%	17.1	11.8	0
Johnson Tacro/ MMF vs. AZA[7]	72	100	23.6/37.5	0	Tacro-MMF-Pred + Ind 36.1%	15.3	4.2	4.2
Global SRL[13]	219	79	N/A	N/A	CsA-SRL 5mg-Pred	19.0	3.0	N/A
US SRL[24]	274	61	23/44	N/A	CsA-SRL 5mg-Pred	14.6	2.9	2.9
Europe MMF[2]	160	100	N/A	7	CsA-MMF 3g-Pred	13.8	2.5	15.0
Miller Tacro MMF 2 dosages vs. AZA[23]	58	100	20.7/56.9	6.9	Tacro-MMF 2 g-Pred + Ind 60.3%	8.6	3.4	6.9
Thymoglobulin vs. ATG[25]	48	73	38/38	8	CsA-AZA-Pred + TMG	4.0	N/A	12.5

Column Abbreviations: N: Number eligible for Intention-to-treat analysis. CAD: cadaveric. AA/NC: African American/Non-Caucasian. Retx: re-transplants. BPAR: Biopsy proven acute rejection at 12 months, * acute rejection at 6 months. SRR: Steroid resistant rejection requiring anti-body therapy. CMV: cytomegalovirus infection (not consistently defined). N/A: Not available.

Therapy Abbreviations: CsA: cyclosporine. Tacro: tacrolimus. Aza: azathioprine. MMF: mycophenolate mofetil. SRL: sirolimus. Pred: prednisone. Ind: ATG or OKT3. ATG: antithymocyte globulin (Atgam). TMG: antithymocyte globulin (Thymoglobulin). Simulect (SIM): basiliximab. Zenapax (ZEN): daclizumab.

of acute rejection can be achieved with different regimens, which then begs the question: Is it possible to achieve the same outcome at a lower cost, or a better outcome at the same cost? Well-designed pharmacoeconomic and outcomes analyses can assist health care decision-makers to identify optimal strategies for patients when selecting among a number of highly effective but costly agents.[17] Utilization of these techniques in combination with the evidence-based medical literature allows one to make both scientifically and economically sound decisions.

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