Chapter 3

Immunosuppressive Drug Therapies

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This chapter reviews the immunosuppressive agents currently used to prevent organ rejection[1] and describes the variation in drug treatment regimens used by transplant recipients. It then discusses the costs associated with various immunosuppressive drug therapies.

IMMUNOSUPPRESSIVE DRUG PROTOCOLS

Components of Immunosuppressive Therapy

Despite the slow but relatively steady development of immunosuppressive products, the number of drugs is still few. Presently, only four drugs are approved by the U.S. Food and Drug Administration (FDA) specifically for post-transplant immunosuppression: azathioprine, cyclosporine, antithymocyte globulin (ATG), and muromonab CD3 (OKT-3) (table 11) (55,56).[2] All four of these drugs are sole-source (i.e., each is produced by only one manufacturer). Prednisone, an adrenal corticosteroid, is also usually administered to patients as part of the immunosuppressive drug regimen and is covered under Medicare for this purpose.

Early approaches to long-term chemical immunosuppression in transplant recipients included a combination of azathioprine (or, after its FDA approval in 1981, ATG) a.ndprednisone. Cyclosporine-based protocols, introduced into general use in 1984, rapidly replaced these approaches to become the mainstay of immunosuppressive therapy in patients who receive organ grafts. The incidence and success rates of heart, heart/lung, and lung transplants increased particularly dramatically in the era following FDA approval of cyclosporine (58). For kidney transplants, cyclosporine use apparently also reduced mortality and morbidity to levels significantly lower than the conventional protocols (7,23,29,43).

Orthoclone OKT-3 (the brand name of muromonab CD3, a monoclinal antibody) is a relatively recent addition to the roster of immunosuppressive agents. OKT-3 is approved by the FDA for the treatment of acute rejection of transplanted organs. However, it has also been used prophylactically (i.e., to prevent organ rejection) by some treatment programs as a replacement for ATG (15). To date, prophylactic OKT-3 therapy has been administered to inpatients, but outpatient administration is not beyond the realm of possibility.

Antilymphocyte globulin (ALG), a new immunosuppressive developed at the University of Minnesota, is not yet approved for general use by the FDA. Like ATG, ALG is used primarily to reverse particularly severe rejection episodes, but it has also been administered routinely as part of a standard immunosuppressive protocol.

Another promising new drug is FK-506, manufactured by a Japanese firm. FK-506 is a powerful and selective immunosuppressive agent with a mode of action similar to that of cyclosporine (7,33,47,63). The most appropriate place of FK-506 in the post-transplant immunosuppressive drug regimen is still a matter of study and debate. Further investigation is necessary to determine the toxicity, potential benefits, and most appropriate clinical application when compared with cyclosporine (16,45).

At least two other potential immunosuppressive drugs are also under development. One new drug under testing is 15-deoxyspergualin (also known as NKT-01), a relative of the antitumor antibiotic spergualin. NKT-01 has been shown to prolong the graft survival of organ and tissue transplants in rodents (19,44) and is currently in Phase I clinical trials in humans (14). Another new compound, rapamycin, has also shown encouraging potential in the laboratory but has not yet been tested in humans (24).

All current and potential immunosuppressive drugs have associated side effects and complications. For example, despite its major contribution to the improved outcome of human organ transplantation over the past decade, cyclosporine is nephrotoxic; it can cause impaired kidney fiction in both kidney transplant recipients and in patients with normal kidneys who have received transplants of

[1]Immunosuppression is used for other indications as well, such as rheumatoid arthritis and various other immune disorders. These uses are not discussed in this Report.

[2]For a review of the historical developments in clinical and experimental immunosuppression, see references 41 and 46.

Table 11—U.S. Food and Drug Administration (FDA) Approval Status and Medicare Coverage of Post-Transplant Immunosuppressive Drugs

Drug	Brand or common name	Manufacturer/developer	FDA approval date (form of administration)	Medicare coverage
Azathioprine	Imuran	Burroughs Wellcome	Mar. 20, 1968 (oral) July 19, 1974 (IV)	Yes
Antithymocyte globulin	Atgam	Upjohn	Nov. 17, 1981 (IV)	Yes
Cyclosporine	Sandimmune	Sandoz	Nov. 14, 1983 (oral and IV)	Yes
Muromonab CD3	Orthoclone OKT-3	Ortho	June 19, 1986 (IV)	Yes
Prednisone	No brand name	Multiple sources	Multiple forms approved	Yes
Antilymphocyte globulin	ALG	University of Minnesota	Not approved	No
Macrolide antibiotic	FK-506	Fujisawa	Not approved	No

ABBREVIATION: IV = intravenous.

SOURCE: Office of Technology Assessment, 1991.

Table 12—Typical Immunosuppressive Drug Protocols for Kidney Transplant Patients

Drug protocol	Setting and protocol phase: Inpatient initial and rejection phases	Setting and protocol phase: Outpatient maintenance phase
Traditional therapy	PRED + AZA	PRED + AZA
Augmented with ALG or ATG ...	PRED + AZA + ALG/ATG	PRED + AZA
Cyclosporine therapy[a]		
Double-drug	CSA + PRED	CSA + PRED
Triple-drug (with ALG, ATG, or OKT-3)	PRED + AZA + ALG/ATG/OKT-3	CSA + PRED + AZA
Quadruple-drug cyclosporine therapy	CSA + PRED + AZA + ALG	CSA + PRED + AZA

ABBREVIATIONS: PRED = Prednisone; AZA = Azathioprine; ALG/ATG = Anti lymphocyte orantithymocyte globulin; CSA = Cyclosporine; OKT-3 - Orthoclone OUT-3.

aThe terms double, triple, and quadruple drug therapy refer here to the number of drugs administered in the initial or inpatienstage.

SOURCE: Battelle Human Affairs Research Centers, Seattle, WA, Cost *and Outcome Analysis of Kidney Transplantation: The Implications of Initial Immunosuppressive Protocol and Diabetes,* under agreement with the Health Care Financing Administration Cooperative Agreement 14-C-98564/0, August 1989.

other organs (7,42). Hypertension (high blood pressure) after heart transplant is another frequently observed complication of cyclosporine-induced immunosuppression (40).

Many of these side effects are dose-related and can be minimized through the use of multiple-drug approaches to irnrnunosuppression that permit lower doses of individual drugs. Indeed, because of the nephrotoxicity associated with cyclosporine, lower dosages of various immunosuppressive agents are being used in increasingly complicated immunosuppressive protocols.

Variation in Drug Treatment Protocols

Until the clinical introduction of cyclosporine, immunosuppressive drug protocols for kidney transplants, the most cornrnon transplant procedure, were similar across transplant programs in the United States and abroad. The mainstay traditional therapy consisted of a combination of azathioprine and prednisone (table 12).

With the introduction of cyclosporine, a variety of new protocols followed in an effort to maximize immunosuppression while minimizing side effects such as nephrotoxicity and susceptibility to infection. The different preferred drug combinations vary across transplant centers and across individual patients within any particular center (7,21). Because the therapy is tailored to the patient, the mix and dosages of drugs also vary over time in any particular patient, depending on the treatment phase and the patient's physiologic reactions to the drugs.

The drugs administered to a given patient differ according to three possible immunosuppressive treatment phases:[3]

[3]For kidney transplant recipients, chronic renal dysfunction may require yet a different protocol (7).

- *The induction phase* consists of approximately the first 6 weeks of use of immunosuppressive drugs during the immediate, post-transplant period. Treatment is usually on an inpatient basis during this phase, since it is the time when the patient's status is most uncertain.
- *Maintenance treatment,* which is usually administered on outpatient basis, is initiated after the patient's medical condition has stabilized and when the organ function is normal or near-normal.
- *Therapy during acute organ rejection,* which sometimes occurs despite maintenance therapy, is usually a short phase requiring higher dosages and, often, different drugs while the patient is hospitalized (7).

For kidney transplants, cyclosporine has increased the complexity of transplant recipient management; distinguishing between a rejection episode and nephrotoxicity is quite obviously confusing on the one hand and critical on the other.

The improved effectiveness of cyclosporine-based protocols over traditional therapy is reflected in the dramatic shift in the immunosuppressive management of kidney transplant recipients since FDA approval of cyclosporine in late 1983. From 1984 to 1989, the number of cadaveric kidney transplant recipients receiving cyclosporine grew from 73 to 93 percent (17) (table 13). The use of this drug increased even more dramatically for living-donor kidney transplant recipients, from 38 percent in 1984 to 87 percent in 1989. Overall, approximately 90 percent of kidney transplant recipients, regardless of source of graft, received cyclosporine as the primary immunosuppressive agent in 1989.[4]

The percentage of transplant recipients receiving cyclosporine is probably similar for recipients of other organs, since cyclosporine was already known to be the most effective irnmunosuppressive drug when these procedures began to be performed more regularly. In contrast, when kidney transplants were initially performed, cyclosporine had not yet been approved by the FDA. Consequently, physicians

Table 13-Percentage of Kidney Transplant Recipients Receiving Cyclosporine, 1984-89

Year	Source of graft	
	Living donor	Cadaveric donor
1984	38%	73%
1985	53	84
1986	68	90
1987	78	92
1988	80	91
1989	87	93

SOURCE: Health Care Financing Administration, Office of Research and Demonstrations, Division of Beneficiary Studies, 1990.

may have tended to keep patients with older transplants on their original regimens. Moreover, because nephrotoxicity is the most significant side effect of cyclosporine, traditional therapies may be warranted for some kidney transplant recipients.

Despite the predominance of cyclosporine as the primary imrnunosuppressive agent, azathioprine and prednisone remain stable components of both inpatient and outpatient irnmunosuppression (table 14). These drugs continue to be important adjuncts to cyclosporine in most of the therapies currently in use.

COST OF IMMUNOSUPPRESSIVE THERAPY

The variation in cost associated with immunosuppressive agents and protocols is substantial. Costs of cyclosporine maintenance therapy protocols, for example, are much higher than those of traditional maintenance therapy.[5] The reported costs for traditional outpatient therapy using only prednisone and azathioprine were $2 per day in 1988, compared with reported average costs for cyclosporine-based therapies ranging from $9 to $23 per day, depending on the source of information (6,7).

Annual costs are similarly variable across protocols and over time (table 15). In 1988, average annual costs for traditional therapy were reported to be $852 for the first year of outpatient therapy and $793 for the subsequent year in 1988 (7). In contrast,

[4]In general, conventional immunosuppressive therapy is only used by patients who received transplants before the cyclosporine era (i.e., before 1984), or by patients unable to tolerate cyclosporine. Nearly all new patients are now placed on cyclosporine, while very few patients who have been on conventional therapy are converted to cyclosporine, unless unique problems arise (7).

[5]The 1991 average wholesale prices (AWPs) for drugs used in immunosuppressive therapy were: $19.43 for 1,000 5-mg tablets of prednisone (manufactured by Rugby); $87.25 for 10050-mg tablets of azathioprine (Imuran); $209.79 for one 5-ml ampule of 50 mg/ml of antithymocyte globulin (Atgam); $214.20 for one 50-mg oral solution of 100 mg/ml of cyclosporine (Sandimmune); and $522.00 for one 5-ml ampule of 1 mg/ml of muromonab CD3 (OKT-3) (34a). These numbers do not necessarily reflect comparable dosages, but nonetheless the differences in the AWPS among traditional and more recent drugs are striking.

Table 14—Percentage of Transplant Recipients Receiving Specific Immunosuppressive Drugs by Drug Type, 1987-90[a]

Transplant type and setting[b]	Percentage of patients receiving: Cyclosporine	Azathioprine	Prednisone	ALG/ATG	OKT-3	Other drugs and therapies
Heart						
Inpatient	94.7%	91.070	89.2%	26.5%	28.3%	1 .2?40
At 1 year outpatient	NA	NA	NA	NA	NA	NA
Kidney (cadaveric)						
Inpatient	96.9	82.7	*94.0*	28.7	16.0	25.4
At 1 year outpatient	94.0	81.5	*92.5*	1.6	3.3	11.6
Kidney (living-donor)						
inpatient	85.5	81.5	92.9	16.0	8.3	23.5
At 1 year outpatient	84.4	82.3	90.7	1.4	2.5	11.5
Liver						
inpatient	98.5	66.2	90.8	13.2	27.7	44.8
At 1 year outpatient	96.3	67.2	92.3	0.6	2.8	15.3
Heart/lung						
inpatient	92.6	91.2	*73.0*	48.0	32.4	*2.0*
At 1 year outpatient	NA	NA	NA	NA	NA	NA
Lung						
inpatient	83.1	89.2	77.1	41.0	34.9	4.8
At 1 year outpatient	NA	NA	NA	NA	NA	NA
Pancreas						
Inpatient	98.5	98.1	96.3	40.2	32.0	14.1
At 1 year outpatient	99.0	98.6	98.6	14.5	23.5	1.7

ABBREVIATIONS: NA = not available; ALG/ATG = anti lymphocyte or antithymocyte globulin; OKT-3 = Orthoclone OKT-3.
[a]Basedon information about patients transplanted between Oct. 1, 1987and Dec. 31, 1989forwhom information was available. Most recipients received more than one immunosuppressive drug.
[b]Information on immunosuppressive therapy for bone marrow transplant recipients was not available.
[c]The "other" category includes FK-506, cyclophospharnide, trimethoprirn/sulfa, solumedrol, chemotherapy, total lymphoid irradiation, and methylprednisolone.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, Health Resources and Services Administration, Division of Organ Transplantation, 1991.

average costs for cyclosporine double drug therapy (i.e., maintenance therapy with cyclosporine plus predisone) were $5,338 in the first year and $4,025 in the subsequent years. Thus, the simplest cyclosporine maintenance therapy is roughly seven times more costly than the traditional therapy.[6]

These numbers are underestimates of total current ongoing costs, since they do not account for costs associated with such factors as organ rejection, conversion from one protocol to another, and general inflation related to the cost of the drugs. For example, the treatment of organ rejection can add considerably to the frost-year immunosuppressive drug costs of transplant recipients. (For the most part, the added drug costs would be absorbed in the hospital's inpatient payment for Medicare patients. However, rejection episodes would increase outpatient costs to some extent as well.) Nonetheless, the annual costs appearing in table 15 illustrate cost differences across the more common protocols and are reasonable approximations of the 1988 costs of outpatient immunosuppressive protocols.

The differences in the estimates of the average annual costs of cyclosporine therapies deserve note. The higher historical figures cited in table 15 are based on a literature review of published data; the lower Battelle numbers are based on results of a 1989 study done under a cooperative agreement with the U.S. Health Care Financing Adrninistration. Rough cost estimates provided by some transplant surgeons likewise suggest that the earlier published numbers may have been somewhat overstated compared with present costs. (28,32). Based on these opinions and the findings of the Battelle study, a best estimate of the current average annual costs of

[6]Note that the simplest cyclosporine-based protocol is not necessarily the least expensive, since the addition of other drugs could permit the dosage (and thus the cost) of cyclosporine to be decreased.

Table 15-Annual Drug Costs for Immunosuppressive Protocols of Kidney Transplant Patients, 1988a

Immunosuppressive protocol	First year costs			Subsequent year outpatient cost	5-year outpatient totals[b]
	Inpatient	Outpatient	Total		
Traditional therapy:					
Without ATG/ALG while inpatient	$ 95	$ 852	$ 947	$ 793	$4,024
With ATG/ALG while inpatient	10,385	852	11,237	793	4,024
Cyclosporine therapy:[c]					
Double-drug					
Historical[d]	638	8,126	8,764	8,198	40,918
Battelle study[e]	550	5,338	5,888	4,028	21,450
Triple-drug					
Historical[d]	4,034	7,756	11,790	8,227	40,664
Battelle study[e]	4,274	3,899	8,173	3,157	16,527
Quadruple-drug					
Historical[d]	5,626	7,193	12,819	6,870	34,673

[a]Based on a 70-kg person (154 pounds).

[b]Costs are in constant 1988 dollars.

[c]Double, triple, and quadruple drug therapy refers hereto the number of drugs administered in the initial or inpatient phase.

[d]Based on previously published data as reviewed by Battelle Human Affairs Research Center, Seattle, WA.

[e]Based on a recent Battelle study of 99 patients, August 1989.

SOURCE: Battelle Human Affairs Research Centers, Seattle, WA, Cost *and Outcome Analysis of Kidney Transplantation: The Implications of Initial /immunosuppressive Protocol and Diabetes,* under agreement with the Health Care Financing Administration, Cooperative Agreement 14-C-98564/0, August 1989.

cyclosporine-based treatment protocols is $4,000 to $6,000 per year.

A likely reason for lower present than historical cyclosporine costs is that the dosage requirements, and thus the costs, for cyclosporine have declined over time. The added cost of drugs used adjunctively with cyclosporine is apparently not high enough to offset the cost savings from the lower cyclosporine dosages in the protocols using these drugs.

Although the annual therapy-related costs of the cyclosporine protocols are still higher than those of traditional therapy, dramatic improvements in graft survival and decreased complications are also evident (7,23,28). Consequently, the higher therapy-related costs are balanced to some extent with cost savings from preventing complications and episodes of acute rejection. Recent studies have suggested, however, that the initial association of cyclosporine with lower total costs diminishes over time (42). In other words, for grafts surviving beyond several months, the use of cyclosporine may reduce actual costs only slightly.