Chapter 4: Strategies to Reduce Drug Costs

4.1: If drug costs block access to transplantation, a strategy to minimize drug costs is appropriate, even if use of inferior drugs is necessary to obtain the improved survival and quality of life benefits of transplantation compared with dialysis. (*Not Graded)*

4.1.1: We suggest strategies that may reduce drug costs include:

- **limiting use of a biologic agent for induction to patients who are high-risk for acute rejection (*2C*);**
- **using ketoconazole to minimize CNI dose *(2D)*;**
- **using a nondihydropyridine CCB to minimize CNI dose *(2C)*;**
- **using azathioprine rather than mycophenolate *(2B)*;**
- **using adequately tested bioequivalent generic drugs *(2C)*;**
- **using prednisone long-term. *(2C)***

4.2: Do not use generic compounds that have not been certified by an independent regulatory agency to meet each of the following criteria when compared to the reference compound *(Not Graded)*:

- **contains the same active ingredient;**
- **is identical in strength, dosage form, and route of administration;**
- **has the same use indications;**
- **is bioequivalent in appropriate bioavailability studies;**
- **meets the same batch requirements for identity, strength, purity and quality;**
- **is manufactured under strict standards.**

4.3: It is important that the patient, and the clinician responsible for the patient's care, be made aware of any change in a prescribed immunosuppressive drug, including a change to a generic drug. *(Not Graded)*

4.4: After switching to a generic medication that is monitored using blood levels, obtain levels and adjust the dose as often as necessary until a stable therapeutic target is achieved. *(Not Graded)*

CCB, calcium-channel blocker; CNI, calcineurin inhibitor.

Background

A number of cost-saving strategies may offer access to transplantation when the cost of immunosuppressive medication is otherwise prohibitive. The use of generic medications can substantially reduce cost. A generic immunosuppressive medication is a medication that is manufactured and distributed without patent protection, but is structurally identical to the brand-name medication. However, manufacturing, distribution and quality control may differ among pharmaceutical companies. Regulatory authorities generally do not require that the efficacy and safety of generic medications be tested in RCTs. Manufacturers of generic drugs must only prove that their preparation is bioequivalent to the existing drug in order to gain regulatory approval.

However, generic drugs approved by the US FDA have met rigid standards. To gain FDA approval (www.fda.gov/cder/ogd; last accessed March 30, 2009), a generic drug must:

- contain the same active ingredients as the brand drug (inactive ingredients may vary);
- be identical in strength, dosage form and route of administration;
- have the same use indications;
- be bioequivalent;
- meet the same batch requirements for identity, strength, purity and quality;
- be manufactured under the same strict standards of the FDA's good manufacturing practice regulations.

Similarly, the European Agency for the Evaluation of Medicinal Products, also known as the European Medicinal Agency (www.emea.europa.eu/htms/human/raguidelines/datagenerics/biosimilars.htm; last accessed March 30, 2009) defines a generic medicinal product as a medicinal product that has:

- the same qualitative and quantitative composition in active substances as the reference product;
- the same pharmaceutical form as the reference medicinal product;
- bioequivalence with the reference medicinal product demonstrated by appropriate bioavailability studies.

Tacrolimus, CsA, mTORi, MMF, and azathioprine are all available as generics (loosely defined) in many countries around the world. However, the efficacy and the safety of these generics may not always be firmly established by local regulatory authorities charged with approving these agents.

Rationale

- Lack of dialysis facilities may make kidney transplantation the only life-saving therapy available for some patients with CKD stage 5.
- Kidney transplantation is the therapy of choice to treat CKD stage 5, since overall costs are lower, and outcomes and quality of life are better compared to dialysis.
- Cost savings that do not compromise patient safety are beneficial.
- Use of cytochrome P-450 inhibitors, such as ketoconazole and diltiazem, allow therapeutic blood levels of CsA to be achieved at a lower dose, thereby reducing cost.
- Azathioprine can be used to achieve most of the efficacy and safety of MMF, but at a much lower cost.
- An adequately tested bioequivalent generic formulation can lower cost without compromising safety and efficacy of the originally patented formulation.

Chronic maintenance dialysis is not available for many patients in a number of developing countries in Asia, Africa, and South America (59). Patients living in remote areas may not have access to dialysis. Kidney transplantation, especially preemptive transplantation (before the need for chronic dialysis), may be the only viable option for long-term renal replacement therapy in many areas of the world. Transplantation is the most cost-effective form of renal replacement therapy, and offers a superior quality of life compared to dialysis (60). For all of these reasons, there is a growing demand for kidney transplantation in the developing world, and it is imperative that kidney transplantation be affordable. Even where immunosuppressive drugs are available, their high cost may preclude their use if adequate health insurance coverage is not available (61).

Calcineurin inhibitors currently form the backbone of immunosuppressive regimens, but their cost imposes a long-term financial burden on patients in developing countries. Forced discontinuation of CsA due to cost increases the risk of acute rejection and may result in poor long-term outcomes (62).

Calcineurin inhibitors and mTORi (sirolimus and everolimus) are metabolized through the hepatic cytochrome P-450 microsomal oxidase enzyme system. Commonly used drugs such as the antifungal ketoconazole and the nondihydropyridine calcium-channel blocker (CCB) diltiazem are known inhibitors of this enzyme system and increase blood levels of these immunosuppressive drugs. This, in turn, reduces the dose necessary to maintain therapeutic blood levels (63,64).

A number of studies (Table 3) have shown that ketoconazole, when used in a dose of 50–200 mg/day, allows substantial reduction in the daily dose of CsA, tacrolimus and sirolimus, while maintaining therapeutic blood levels (65–76). In a RCT (69), 51 patients received 100 mg/day of ketoconazole along with CsA and 49 served as controls. The dose reduction was highest at 1 month (76.5%) and was maintained at 10 years (64.6%). The cost of CsA decreased by 73% at 1 year, 69% at 5 years and 63% at 10 years in the intervention group, while the decrease in cost was 13% and 20% in the control group at 1 and 10 years, respectively.

In another study (73), 70 patients on a tacrolimus-based immunosuppression regimen were randomly allocated to receive ketoconazole (n = 35) or no ketoconazole (controls, n = 35). The tacrolimus dose reduction was 58.7% at 6 months and 53.8% at 2 years, leading to cost reduction of 56.9% and 52.2%, respectively. None of the studies has reported any adverse effect of this approach on graft function.

Ketoconazole requires an acidic milieu in the stomach for its absorption; hence, concomitant use of agents that inhibit gastric acid secretion should be avoided.

In comparison to ketoconazole, the dose reduction achieved with diltiazem is modest (67,77). Hence, some would suggest that a nondihydropyridine CCB, such as diltiazem, be used only in situations where ketoconazole is

Table 3: CNI cost reduction from the concomitant use of ketoconazole

Study	CNI	Keto (N)	Control (N)	Mean follow-up (months)	Ketoconazole (mg/day)[a]	Estimated cost reduction (%)
First (66)[b]	CsA	24	28	15	200	73
Butman (66A)	CsA	15	–	11	400	72
Keogh (68)[b]	CsA	23	20	25	200	80
Sobh (69)[b]	CsA	51	49	53	82.8	73
Carbajal (71)	CsA	14	17	29	54 ± 17	60
El-Dahshan (73)[b]	Tac	35	35	24	100	53
Soltero (73A)	Tac	11	–	15	87	78

CNI, calcineurin inhibitor; CsA, cyclosporine A; Keto, ketoconazole; Tac, tacrolimus.
[a]Fixed total once daily dose, or mean ± standard deviation.
[b]RCT

contraindicated. On the other hand, if patients discontinue ketoconazole abruptly, the levels of immunosuppressive drugs may drop precipitously and result in acute rejection. A precipitous drop is less likely with nondihydropyridine CCBs, and the risk of acute rejection may therefore be less. In addition, most KTRs have hypertension that requires treatment, and nondihydropyridine CCBs may serve the dual purpose of treating hypertension and reducing cost. The choice between ketoconazole and a CCB should be adapted to the patient's situation and preference.

The use of 2-h CsA concentration (C_2) monitoring for adjusting drug dose is not suitable for patients receiving ketoconazole or diltiazem. Metabolic inhibitors interfere with the disposal—but not the absorption—of CsA or tacrolimus, and therefore flatten the AUC. In this situation, the CsA AUC correlates better with C_0 than C_2. Dose adjustments based on C_2 levels may lead to CsA toxicity (78). Trough concentration monitoring therefore should be used to adjust drug dosage.

Although MMF is considered the preferred antimetabolite for KTRs, the Mycophenolate Steroid Sparing follow-up study showed that azathioprine-treated patients experienced similar long-term outcomes compared to those receiving MMF after a median 5.4 years (37). CsA-ME was the CNI used in this study. The length of hospital stay, incidence of acute rejections, and the likelihood of return to dialysis were also similar in the two groups. In a cost-minimization analysis, MMF was found to be 15 times more expensive than azathioprine. This study (and the lack of large differences in outcomes in other studies comparing MMF with azathioprine) suggests that it may be acceptable to use azathioprine in place of MMF when cost is an important consideration.

A number of generic formulations of CsA, tacrolimus, mTORi and MMF are now available around the world. Generic formulations vary from country to country. Most countries require evidence of bioequivalence in only a small number of patients before marketing is permitted. In many countries, however, generic formulations have been available for over 10 years and their efficacy has been established in real-life situations. Head-to-head data comparing efficacy and toxicity are generally not available for most generics (79–81). Caution should therefore be exercised in choosing a generic formulation for use in KTRs. Ideally, a generic formulation should be used only after its safety and efficacy have been established in KTRs.