

*Editorial*

## **Reducing the Cost of Renal Transplantation in Developing Countries**

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Chronic Kidney Disease has become a major health problem in developing countries. The incidence of End-stage Renal Disease (ESRD) in some African and Middle East countries ranges from 110 to 300 patients per million population (pmp) per year [1,2]. With limited dialysis facilities in many developing countries, renal transplantation in addition to being the definitive treatment for ESRD offers less expensive and more practical modality for renal replacement therapy

Although less expensive than dialysis in the long-term, renal transplantation is still beyond the financial capabilities of many developing countries. Accordingly all measures to reduce its cost need to be considered without compromising the quality of care.

At present there are a number of measures which are known to contribute to the reduction of the transplant cost without jeopardizing the outcome. These measures are discussed below.

Although the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients recommends induction therapy with a biologic agent for all patients, to reduce the cost in developing countries the guideline recommends only using induction therapy in patients with high risk for rejection [3].

Of the antiproliferative agents azathioprine may be used instead of mycophenolate. The therapeutic superiority of mycophenolate over azathioprine is controversial: some randomized controlled trials (RCTs) have shown

that mycophenolate is significantly better in preventing acute rejection than placebo [4,5] but in general RCTs comparing outcomes between mycophenolate and azathioprine have shown significant inconsistencies. In a meta-analysis of 19 trials with 3143 patients mycophenolate was associated with less acute rejection and improved graft survival compared to azathioprine but there were no differences in patients' survival or renal function [6]. In addition there were no differences in major adverse effects but diarrhoea was more common with mycophenolate. A group of other RCTs showed less acute rejection with mycophenolate compared to azathioprine but the difference was not statistically significant and even some other trials did not show any difference between the two therapeutic agents [7,8].

Another measure to reduce the cost of renal transplantation is the use of cytochrome P-450 inhibitors which augment the effect of calcineurin inhibitors such as ketoconazole and the nondihydropyridine calcium channel blocker diltiazem. This beneficial effect has been confirmed in more than eight RCTs which were started in the early 1990s; some of these trials continued for more than 10 years. In this respect ketoconazole is superior to diltiazem, achieving cost reduction amounting to 73% and 63% in the first and fifth years respectively compared to only a modest reduction by diltiazem [9]. The earlier skepticism about the long-term adverse effects of ketoconazole has mostly been alleviated by the results of RCTs that had continued for more than 10 years without showing adverse effects [9]. There may be more justification for the use of ketoconazole in the early post-transplant course when the required doses of calcineurin inhibitors are high; this reduction in cost may decrease with the lower doses of

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calcineurin inhibitors used in the long-term maintenance. There are some precautionary measures which need to be observed with the use of ketoconazole: the acidic milieu required for its absorption makes the concomitant use of proton pump inhibitors undesirable. In addition the need to stop ketoconazole for any reason may cause sudden drop in the level of calcineurin inhibitors leading to acute rejection episodes if the required dose adjustment is not closely observed.

The use of generic calcineurin inhibitors, mTOR inhibitors and mycophenolate can substantially reduce the cost of renal transplantation but should be practiced with caution. Many generics have been available for many years and their efficacy has been established with actual use but head-to-head data comparing efficacy and toxicity are not available for most generics. The United States Food and Drug Administration and the European Medicinal Agency have issued strict regulations for the use of generic medications stressing that the generic formulation should have the same qualitative and quantitative composition and the same bioequivalence as the reference product. Adherence to such regulatory measures is vital if generic medications are to be used for renal transplant recipients

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