Improving Medication Adherence and Outcomes in Transplant Recipients

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Abstract Nonadherence of transplant recipients to prescribed medical regimens is a major cause of allograft failure. Significant nonadherence, which occurs in approximately 22% of renal allograft recipients, may be a component of allograft loss in an estimated 36% of patients. It is associated with an increased rate of both acute and chronic rejection and, accordingly, decreased renal allograft survival with the consequent reinstitution of renal replacement therapy. The economic impact of nonadherence is great. The identification of risk factors plus measures to address them effectively can have a significant medical, social, and economic impact. Further advances to improve medication adherence depend upon improving interactions between patients and caregivers, broadening immunosuppressant availability, simplifying medication regimens, optimizing medication profiles, and taking advantage of new technology.

According to the World Health Organization, adherence is “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with the agreed recommendations from a healthcare provider.” Among transplant recipients, nonadherence, also referred to as “noncompliance,” is a major risk factor for rejection and allograft loss. A report from a consensus conference on nonadherence to immunosuppressive agents concluded that nonadherence is more prevalent than previously assumed, difficult to measure accurately, linked to worse outcomes, the result of various factors, and difficult to change from a behavioral perspective.

In a meta-analysis, Dew et al1 found medication nonadherence across all organ transplants to be 22.6 cases/100 patient-years. Systematic reviews demonstrated that an estimated 50% (range, 20%–73%) of late acute allograft rejections and 15% (range, 3%–35%) of graft losses are associated with medication nonadherence.2 Pinsky et al6 identified an increase of $12,840 (in US currency) in individual 3-year medical costs for patients who exhibit persistently low compliance. Despite these discouraging data, Cleemput et al7 reported that renal transplantation is more cost-effective than is hemodialysis, even if patients are nonadherent post transplantation, and that renal transplantation offers an improved quality of life (QOL) and increased survival.

Although nonadherence is a complex and challenging problem, understanding its basis may help to improve transplant outcomes. This review is based on a satellite symposium conducted during the 2013 American Transplant Congress held in Seattle, Washington. The speakers were Flavio Vincenti, MD, Clinical Professor of Medicine and Surgery and Deborah Faiman Endowed Chair in Kidney Transplantation at the University of California at San Francisco in San Francisco, California, and Ron Shapiro, MD, Professor of Surgery, The Robert J. Corry Chair in Transplantation Surgery and Associate Clinical Director at the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh in Pittsburgh, Pennsylvania.

Impact of Medication Nonadherence

Nonadherence to immunosuppressive drug regimens is defined as a deviation from the prescribed medication plan sufficient to influence the regimen’s intended effect adversely. Post-transplant nonadherence is common, ranging from 5% to > 45% of patients.6 Nonadherence rates increase dramatically > 6 months post transplantation. Accurately quantifying nonadherence can be difficult because of inconsistent methodology. Many studies are based on patient self-reporting, and highly variable response rates are likely to underestimate nonadherence. Nonadherence adverse effects on transplant outcomes include rejection episodes, graft loss, and consequent resumption of dialysis.

Butler et al8 performed a meta-analysis of 36 cross-sectional and cohort studies and case series. Odds of graft failure increased sevenfold in nonadherent subjects when compared with adherent subjects (odds ratio = 7.1; 95% confidence

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interval, 4.4–11.7; \( P < 0.001 \). The authors suggested that standardized methods to assess medication adherence in clinical populations must be developed and that future studies should try to identify the level of adherence that increases the risk of graft failure. Furthermore, they noted that since nonadherence is common and greatly impacts transplant survival, institution of effective interventions to improve adherence may provide significant improvements in graft survival.

Vlaminck et al\(^9\) monitored adherence among 146 adult kidney recipients. Patients were considered to be noncompliant if they admitted to skipping immunosuppressant medication regularly over the previous 12 months. In all, 22.6% of these kidney recipients were considered to be noncompliant, of which 21.2% experienced a late acute rejection, as compared with 8% of the adherent group at 5 years (\( P < 0.05 \); Figure 1). Nonadherent patients demonstrated progressive worsening of renal function over time, even in the absence of acute rejection. They also were more likely to demonstrate markers of antibody activation at biopsy than were adherent patients with renal dysfunction, and the histology in nonadherent individuals revealed substantially more interstitial fibrosis and tubular atrophy than in medically compliant patients.

Likewise, Sellarés et al\(^10\) followed 315 allograft recipients who underwent indication biopsies at 6 days to 32 years after kidney transplant. A total of 60 kidneys progressed to failure during the follow-up period (median, 31.4 months). Such failure occurred rarely after T-cell–mediated rejection and acute kidney injury; it was common after antibody-mediated rejection or glomerulonephritis. Among patients who experienced rejection losses, 17 of 36 (47%) were independently identified as being nonadherent by attending physicians (Figure 2).\(^{10}\) Furthermore, nonadherence was identified in 32% of patients who progressed to renal failure and just 3% of those who survived.

**MEASURING NONADHERENCE**

The gold standard for measuring adherence to oral medication remains electronic medication monitoring with a microdevice that records each time a medication bottle is opened. Limitations of this method, however, include lack of certainty that the medication or correct dose was ingested and lack of availability of these devices and the means to monitor and record their data in clinical practice. Patient self-reporting has inherent limitations. For example, patients may not be willing to disclose nonadherence, even in nonthreatening circumstances. Prescription refill rates correlate with adherence, but they may be difficult to monitor in clinical practice, and they reveal nothing about timing of ingestion. A potentially useful metric is drug-level monitoring when used as a surrogate for compliance.

**NONADHERENCE BEHAVIORAL PATTERNS**

Behavioral patterns of nonadherence should be evaluated to reduce nonadherence in the future, help physicians understand patients’ clinical outcomes, develop evidence-based screening tools for patients who are most likely at risk of being nonadherent, and design interventions to help prevent nonadherence in the patient population.

**Identifying Nonadherent Patients**

Little is known about why patients do not adhere to their immunosuppression regimens. Greenstein and Siegal\(^11\) identified three groups of noncompliers:
accidental noncompliers (47%), invulnerable noncompliers who had a belief of invincibility (28%), and decisive noncompliers (25%). Each of these groups has different origins and requires different interventions. Other common reasons for noncompliance include oversleeping, experiencing work-related barriers and forgetfulness, forgetting to refill medications, and traveling without medication.

**Difficulties with Adhering to Prescribed Drug Regimens**

Increasing frequency of drug doses increases nonadherence. Beckebaum and others examined efficacy, safety, and immunosuppressant adherence in 125 stable liver transplant patients who switched from twice-daily tacrolimus to once-daily tacrolimus. Decreasing the dosing frequency of tacrolimus from twice daily to once daily reduced the nonadherence rate from 66.4% at study entry to 30.9% post conversion (P < 0.0001). The prevalence of nonadherence at baseline was significantly higher among patients who converted > 2 years after liver transplant and in those ≤ 60 years of age. The authors concluded that converting such patients to once-daily tacrolimus is safe and is related to enhanced immunosuppressant adherence; however, clinicians should closely monitor the patient’s whole-blood tacrolimus level during the initial dosing period.

**The Problem of Adverse Effects**

Side effects also contribute to nonadherence. In a prospective, longitudinal, single-center study by Toledo and colleagues, 31 liver transplant patients who were treated with mycophenolate mofetil and had gastrointestinal (GI) disturbances post transplant were converted to equimolar enteric-coated mycophenolate sodium. After conversion, significant improvement was noted in their overall Gastrointestinal Symptom Rating Scale score from baseline to 1 month and 3 months, with significant reductions in all subgroups except the GI reflux subgroup. A significant increase in health-related QOL was noted in the overall Gastrointestinal Quality-of-Life Index between 1 month and 3 months, among all subgroups except the social functioning and medical treatment subgroups showing significant improvements (Figure 3).

**Access to Immunosuppressants and Financial Considerations**

Access to immunosuppressive agents is a prerequisite to medication adherence. Financial distress is another important contributing factor to nonadherence. Woodward et al. investigated whether Medicare’s extension of maintenance immunosuppressants from 1 to 3 years following renal transplantation would improve graft survival among low-income transplant recipients. The investigators merged patient-level clinical data from the US Renal Data System (USRDS)-distributed United Network for Organ Sharing (UNOS) registry of kidney transplants throughout the United States with median family income for each patient’s ZIP code according to the 1990 census. They merged median incomes to 10,837 first cadaveric renal transplants performed between 1992 and 1993 and 16,732 transplants performed between 1995 and 1997. Each chronologic cohort was divided into three medication-related beliefs to be most predictive of noncompliance.

The investigators found no differences in graft survival at 1 year for either period between the groups. When immunosuppressants were covered by Medicare for only 1 year, however, the low-income group of 1-year graft survivors had 4.5% lower graft survival at the end of 3 years following transplant. From 1994 to 1997, when Medicare provided 3 years of immunosuppressant coverage, low- and high-income groups had equivalent graft survival 3 years after transplant was accomplished.

**The Effect of Age**

Age predicts adherence patterns. In a large, multicenter study designed to identify variables that affect the likelihood of adherence to immunosuppressive medication regimens and distinguish among compliant patients, Greenstein and Siegal discovered that 22.4% of 1,402 respondents were noncompliant. A logistic regression model showed age, occupation, time since transplant, and three medication-related beliefs to be most predictive of noncompliance.

Pinsky and others described factors associated with compliance to immunosuppression after kidney transplantation and examined relationships between compliance, allograft outcomes, and
CONCLUSION

IMPROVING PATIENT ADHERENCE TO MEDICATIONS

Successful intervention to improve adherence requires a team approach. Combining strategies at the patient, healthcare provider, setting, and system levels may be effective in the long term.

Monitoring Pretransplant Patterns

Before transplantation, there are relatively few evidence-based guidelines available for screening adherence. Because nonadherence to dialysis regimens may predict similar behavior post transplantation, it is not unreasonable to delay transplantation until a patient demonstrates adherence to a dialysis regimen.

Providing Patient Education

Educating patients about the importance of taking immunosuppressive agents as directed must be an ongoing effort. Some centers use repetitive teaching to promote adherence.

Simplifying Dosing Regimens

Another method to improve adherence is to simplify dosing regimens. Clinical trials have shown that use of recently introduced biologic agents, such as belatacept, given as chronic maintenance therapy via monthly infusions is associated with excellent adherence.15

Using Social Media and Technology

Social media (eg, Facebook, Twitter) and cutting-edge technology (eg, smartphone applications, tablets, and pocket-sized personal computers) are proving crucial in improving medication adherence, especially among the younger population.

In a prospective study, Miloh et al16 sent text-message reminders to pediatric transplant recipients or their caregivers; they then compared patient records for the year before and the year of the study and used the standard deviation of serum tacrolimus levels as an indicator of adherence. A total of 41 patients (median age, 15 years [range, 1–27 years]; median age at transplantation, 2 years [range, 4 months to 23 years]) provided consent. In all, 29 of the patients self-administered medications. Twenty-two patients received one immunosuppressant, 14 received two agents, and 5 received three drugs. The investigators found a significant improvement in medication adherence and outcomes for pediatric liver transplant recipients when text messaging was implemented, with the number of acute cellular rejection episodes decreasing from 12 to 2 during the study.

Providing Benefit Assistance

Finally, the availability of social workers to help access benefits also can enhance adherence to immunosuppressive drug regimens.

REFERENCES


