Nonadherence to Immunosuppressive Medication: New Insights

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Abstract Nonadherence to medical instructions is a huge problem for the organ-transplant community. A number of risk factors for nonadherence have been identified. A satisfactory solution to this problem remains elusive, although manipulation of dosing schemes and switching from immediate-release to controlled-release drug formulations may lead to greater compliance among patients who have received a tissue transplant.

Nonadherence to immunosuppressive medication is one of the major, most preventable causes of late graft loss. However, investigation of nonadherence and its risk factors is difficult. The prevalence of nonadherence may be as high as 23% across all solid-organ transplant groups. From 15%–60% of late acute graft rejections are associated with nonadherence, as are 5%–36% of grafts in solid-organ transplant patients.

This year at the American Transplant Congress, many studies highlighted during poster sessions tackled the issue of nonadherence and ways to improve outcomes. Among strategies being studied are switching from immediate-release to extended-release tacrolimus and reducing the frequency of administration of this common immunosuppressant from twice daily to once daily.

Tools and Definitions of Nonadherence
A variety of tools and definitions have been used to address nonadherence to prescribed medical regimens. In the setting of transplantation, medical noncompliance or nonadherence has been defined as a “deviation from the prescribed medication regimen sufficient to adversely influence the regimen’s intended effect.” Direct measures of adherence include observation of medication intake and biologic assay of drug levels or drug metabolites in the blood or urine. Indirect measures include patient self-reporting, collateral reports from family members or clinicians, prescription fills, pill counts, and electronic monitoring.

In comparison with electronic monitoring as a reference standard, no one tool related to investigation of medical noncompliance demonstrates both a high sensitivity and specificity. However, several survey instruments and other tools have been used in the study of this phenomenon; often, they are used with another direct or indirect measure.

Adherence Scales
The Immunosuppressant Therapy Adherence Scale (ITAS) is a five-item questionnaire that investigates how often patients are noncompliant with immunosuppressive medications. This survey instrument was validated in 2005, when Chisholm and others compared scores of 222 patients with clinical indicators of adherence, including refill record adherence rates, serum immunosuppressant concentrations, graft rejection, and increased serum creatinine levels.

Another tool, the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS), examines dosing habits over 4 weeks. Patients record information on several factors, such as adherence in taking the medicine, dosing on schedule, having drug holidays, and reducing doses.

Why Are Some Patients Nonadherent to Therapy?
Serper et al examined the topic of medical nonadherence among the transplant population in the context of medical misunderstanding. They conducted a cross-sectional study of 192 liver and kidney recipients and interviewed each patient to assess demographics, health literacy, cognitive function, social support, medication adherence, and ability to fill a pill tray. They determined adherence via self-reporting and measurement of serum tacrolimus levels. Ultimately, the identified risk factors of nonadherence were poor scoring on the health literacy test, older age, greater complexity of the medical regimen, and time span < 2 years since transplant.

Sanders-Pinheiro et al conducted a cross-sectional study of 100 kidney recipi-
Nonadherence to immunosuppressive medication is the major reason for late graft loss among kidney-transplant recipients, especially among younger patients.

Summary

Of five studies specifically examining nonadherence to immunosuppressive medication, only one looked into both liver and kidney transplants; the rest involved kidney transplants only. Two studies were cross-sectional, two were retrospective, and one was prospective. One used the ITAS questionnaire along with extensive interviewing. One used the BAASIS questionnaire as well as collateral information and immunosuppressant blood levels. One defined noncompliance as 7 days without immunosuppression and/or three consecutively missed clinic appointments in 1 year. One study used self-reporting of nonadherence and immunosuppressant blood levels. Finally, the one prospective study used competing-risks methodology to determine the likelihood of graft failure secondary to noncompliance.

Nonadherence was found in 24%–51% of patients across the five studies. This explanation was the most common reason for late graft loss in the two studies that commented on it.

Summarizing the findings of these studies is difficult, since tools used to measure medication nonadherence varied along with the results. Two studies found that younger age was a risk factor. Age < 50 years was related to nonadherence in one study, and age < 35 years was noted in the other. The study finding age < 35 years to be a risk factor also listed being non-white as a determinant—the risk of developing graft failure from noncompliance was 28% among non-whites who were < 35 years old. In addition, white patients > 50 years old had a 0% chance of developing graft failure due to noncompliance. One group of investigators concluded that older age was a risk factor for noncompliance. Another study that involved in-depth interviews with patients to examine differences in health literacy, cognitive function, social support, and adherence to and understanding of medication dosing schedules proposed that limited health literacy was a risk factor. In addition, greater complexity of drug regimens and having undergone transplant surgery ≤ 2 years before being interviewed were identified as risk factors.

■ IS REGIMEN SIMPLIFICATION THE ANSWER?

Simplifying the medication regimen was an idea echoed in studies examining...
alternative formulations of both mycophenolate mofetil (MMF) and tacrolimus.

**Mycophenolic Acid Observational Renal Transplant (MORE) Study**

Conducted at 40 sites in the United States, the MORE study was a 4-year, prospective study that compared adherence among patients using enteric-coated mycophenolate sodium (EC-MPS) or MMF. This study also used the ITAS questionnaire and defined nonadherence as a score < 11. In all, 49.7% of patients were nonadherent at some point, and individuals taking EC-MPS were more likely to score better on the ITAS and to maintain their prescribed dose of medication at 1 year. Age, gender, and delayed graft function were not risk factors for nonadherence, although being black was.

**Manipulating Tacrolimus Dosing**

Simplifying the dosing regimen for tacrolimus is another option. Several studies have compared the use of a once-daily tacrolimus formulation with twice-daily standard tacrolimus to assess the safety and efficacy of the once-daily formulation and whether compliance improved among patients who used it.

Cantarovich et al undertook a multicenter longitudinal study over 6 months that included 1,190 patients. The investigators obtained clinical data and had patients complete a self-questionnaire at 0, 3, and 6 months. Only 7% of study patients were given once-daily tacrolimus immediately after surgery, whereas the rest were switched from twice-daily to once-daily tacrolimus during follow-up (mean, 4.8 years). An evaluation of medication adherence by questionnaire showed that use of once-daily tacrolimus increased compliance by 20%. Further, only 10.5% of patients required a dose change. Just four patients (three kidney transplant recipients and one liver transplant recipient, or < 1% of the study population) experienced an acute rejection episode. There was no control group for this study.

The prospective, randomized, controlled TAESR trial compared adherence to once-daily versus twice-daily tacrolimus administration after alemtuzumab induction and rapid corticosteroid elimination at 7 days. In all, 50 patients were examined at 1 year. Graft rejection-free survival was the same across both treatment groups (survival with a functioning graft at 1 year, 96% for standard-release tacrolimus vs 92% for extended-release; rejection-free survival, 84% for standard-release tacrolimus vs 86% for extended-release tacrolimus). No significant differences between the two groups were found in mean graft function, tacrolimus levels, tacrolimus trough levels, or subclinical graft rejection (as assessed by biopsy at 3 months and 1 year).

Harada et al looked into once-daily tacrolimus dosing, finding that doubling the dose of twice-daily tacrolimus was not necessary. They retrospectively looked at 121 kidney-transplant recipients, with half taking twice-daily tacrolimus and half using the drug once daily in addition to MMF, basiliximab, and corticosteroids. (High-risk patients were given rituximab as well.) Initially, daily tacrolimus doses were adjusted according to the area-under-the-curve (AUC) of tacrolimus over 24 hours, which initially was considered to be twice the AUC over 12 hours of twice-daily tacrolimus. However, seven patients dropped out of the once-daily tacrolimus arm because of a “presumably adverse event.” The investigators then reduced the target tacrolimus AUC to 60% of the initial level in the daily-dosing group. At 1 year, the number of acute rejections, opportunistic infections, and cases of biopsy-proven calcineurin nephrotoxicity at 1, 6, and 12 months were the same. Patients taking the daily-tacrolimus regimen had less glucose intolerance at 1 year.

Oh et al performed a multicenter, randomized clinical investigation of 60 patients to establish the safety and efficacy of once-daily tacrolimus. One month postoperatively, patients either were maintained on twice-daily tacrolimus or switched to the daily extended-release formulation; they then were followed for 6 months. At 5 months, biopsy-confirmed rejection was 0% among the group given daily tacrolimus and 10.7% among patients given twice-daily dosing. There were no differences between the two groups in patient survival (100%), glomerular filtration rate, or safety and satisfaction profiles.

**Comparing Grafts from Different Donor Types**

Andrés et al investigated the efficacy and safety of extended-release tacrolimus among renal transplant recipients who received grafts from various types of donors (standard criteria, extended criteria, and donation after cardiac death). They followed 153 consecutive renal transplant patients for 1 year. Patients began using extended-release tacrolimus immediately after transplant surgery. There was no difference in tacrolimus levels; at 1 year, graft survival was 91% and patient survival, 95%. Acute rejection was low in all groups, but it was highest in the group given grafts from standard-criteria donors, which had the most hyperimmunized subjects.

**Summary**

Of the five studies that looked into extended-release tacrolimus, two were prospective randomized trials, two were retrospective, and one was a multicenter longitudinal trial. All but one found that tacrolimus dosing and serum levels were similar when patients taking tacrolimus once daily were compared with those using twice-daily dosing. Rates of acute cellular rejection were low for both groups, and graft and patient survival also were equivalent. One study reported a 20% improvement in compliance with use of the once-daily formulation.

Ultimately, data from studies looking into tacrolimus showed that a reduction in dosing from twice-daily to once-daily administration by switching to an extended-release formulation of the drug can be accomplished safely and effectively as long as serum trough levels of tacrolimus are reviewed regularly. Whether or not such a switch would improve compliance was examined in one large trial with 1,190 participants. The results of this study suggested that use of the once-daily formulation would be beneficial.

**REFERENCES**

Summertime 2013

THE IMMUNOLOGY REPORT


