LEADING ARTICLE

Drugs 2002; 62 (4): 567-575
0012-6667/02/0004-0567/$30.00/0

Issues of Adherence to Immunosuppressant Therapy After Solid-Organ Transplantation

Marie A. Chisholm

Department of Clinical and Administrative Sciences, University of Georgia College of Pharmacy and Department of Medicine, Medical College of Georgia, Augusta, Georgia, USA

Abstract

Nonadherence to immunosuppressant therapy constitutes a major barrier to post-transplant care. Failure of transplant recipients to take prescribed drugs properly may not only be a significant obstacle to optimal graft function but it may also result in decreased quality of life and productivity, increased morbidity and healthcare cost, and death. Despite the obvious importance of adherence to immunosuppressant therapy, nonadherence is frequent among transplant recipients, with rates ranging from 2 to 68%.

This manuscript briefly discusses several issues concerning adherence to immunosuppressant therapy of solid-organ transplant recipients; presents a literature review concerning adherence to immunosuppressant therapy by solid-organ transplant recipients; and suggests strategies that may be used to enhance medication adherence. Although many of the studies have results that conflict concerning factors associated with immunosuppressive nonadherence, most of the investigators concluded that nonadherent behaviour is usually not predictable. Because of possible adverse events, emphasis should be placed on increasing medication adherence in all transplant recipients.

1. Importance and Consequences of Nonadherence to Immunosuppressant Therapy

Transplantation is a valuable treatment for many organ diseases. However, graft survival depends on the adherence of the recipient to immunosuppressant therapy. Nonadherence to immunosuppressive therapy is a leading cause of graft rejection. Many transplant recipients do not take their therapies as prescribed, and may subsequently experience graft loss or death as a result. Failure of transplant recipients to take prescribed drugs properly may not only be a significant obstacle to graft maintenance, but it may also result in dialysis, decreased productivity, reduced quality of life, and increased morbidity, mortality and healthcare cost. Despite the apparent importance of adherence to immunosuppressive therapy, nonadherence is frequent among transplant recipients. The purpose of this manuscript is to concisely:[1] discuss several issues concerning adherence to immunotherapy in solid-organ transplant recipients;[2] present a literature review concerning adherence to immunosuppressant therapy in solid-organ transplant recipients; and[3] suggest strategies that may be used to enhance medication adherence.

2. Medication Adherence Measures

Before discussing measurements of medication taking behaviour, it is important to discuss terms used to describe this type of behaviour. One of the fundamental issues of controversy is the distinction between the terms compliance and adherence. Traditionally, compliance has been characterised as the extent patients follow instructions provided by their physicians.[1] Whereas, the term adherence implies that patients take a more active, voluntary and collaborative involvement in their healthcare.[2] Since both compliance and adherence refer to medication taking behaviour and because many studies equate these terms, in this manuscript the terms compliance and adherence are used interchangeably.

Although numerous methods for measuring medication adherence are available, accurate measurement of adherence is difficult. The ideal method of measurement should be simultaneously objective, practical and unobtrusive.[3] Direct methods for measuring adherence provide evidence that the medication has been taken by the patient and include blood drug concentration monitoring, urine assay for drug metabolite, detection of a biological marker that is given with or influenced by the drug, and direct observation of drug administration. Most of the methods used to assess adherence are indirect methods and include patient self-reports, dose quantitation (e.g. pill counts, electronic monitoring devices), and review of prescription records. No one method is without limitations nor is any one method superior in all aspects to another. Table I presents the advantages and disadvantages of methods used to measure medication adherence.

3. Studies on Adherence with Immunosuppressive Therapy

The studies presented in table II result from a literature search of immunosuppressant adherence studies published over the last 14 years.[5-18] In order to be included in table II, the study had to involve solid-organ transplant recipients, report an immunosuppressant medication adherence rate, and describe factors that were associated with adherence (or nonadherence). Since kidney transplants are more common than any other solid-organ transplant, most of the individuals in the studies are kidney transplant recipients; however, all types of solid-organ transplants are represented in the table.

One of the difficulties of evaluating drug adherence studies concerns the differences in methodologies used to measure adherence. The most com-

Table I. Advantages and disadvantages of methods used to assess medication adherence. Adapted from Stewart and Caranasos[4]

Method	Advantages	Disadvantages
Blood concentration monitoring	Provides an objective measure and is usually quantitative	Expensive and inconvenient to patient
		Limited range of drugs available for monitoring
		Possibility of laboratory error or timing of blood sample
		Patient may increase compliance prior to blood draw
Electronic monitoring devices	Provides an objective measure of quantity dispensed	Expensive
		Assumes only one source of medication supply
		Assumes medication dispensed was consumed
Patient interview direct questioning	Inexpensive	Depends on memory and honesty of patient
	Immediate feedback	Depends on skills of interviewer
Pill count	Provides objective measure of quantity taken	Time consuming
		Assumes medication not in container was consumed
Refill record	Provides an objective measure of quantity medication obtained	Assumes only one source of medication
Urine assay for measure of drug metabolites or marker compound	Objective measure	Usually a qualitative indication of drug consumption
		Depends on reliability of assay
		Patient may increase compliance prior to urinalysis

Table II. Studies of medication nonadherence or noncompliance among adult solid-organ transplant recipients

Reference	Research design	No. pts/ selection criteria	Measures of noncompliance	% Noncompliant	Factors associated with noncompliance	Clinical consequences of noncompliance
Didlake et al. (1988)[5]	Record review and mail questionnaire	531; mail survey subset = 185 receiving CsA	Major: CsA serum <25 μ g/L and graft loss	Major NC: 3%	*Major NC* associated with African-American race	The 15 patients showing major NC had graft loss.
			Minor: CsA serum <25 μ g/L and rejection episode	Minor NC: 2%	*Minor NC* associated with female sex and Caucasian race.	
			Subclinical: survey indicated missed CsA or prednisone	Subclinical: 16%		
Rovelli et al. (1989)[6,7]	*2 record reviews*: S_1-retrospective, S_2-prospective	n_1 = 260 n_2 = 196 Functioning graft ≥3m after tx	Patient reports in medical records	S_1- 18% S_2 - 15%	NC ↑ in those <20yr of age compared with those >40yr; NC ↑ with ↓ SES.	S_1 = 91% of those who are NC with both follow-up and therapy either experienced a rejection or died compared with 18% of compliant patients. S_2 = 30% of the NC patients experienced a rejection or died compared with 1% of the compliant patients.
Schweizer et al. (1990)[8]a	*3 record reviews*: S_1-retrospective, S_2-prospective, S_3-prospective follow-up of S_2	n_1 = 260 n_2 = 196 n_3 = 82 Functioning graft ≥3m after tx	Patient reports in medical records	S_1 - 18% S_2 - 15% S_3 - 2%	NC ↑ in those <20yr of age compared with those >40yr and in those with ↓ SES. NC higher in Blacks and Hispanics, and Blacks compared with non-Hispanic whites. NC usually not predictable and often without identifiable cause.	
Butkus et al., (1992)[9]	Record review	100 ≥1yr after tx; receiving CsA	Missed ≥3 consecutive clinic visits; ≥2 consecutive CsA serum concentrations undetectable; left hospital against medical advice	African-American: 16% Caucasian: 2%	African Americans: NC ↑ if no private insurance; Caucasians: insurance status not related to NC	NC contributes to reduction in long term graft survival rates.
Kiley et al., (1993)[10]	Retrospective record review	105 ≥18m after tx	Serum CsA concentrations <30 μg/L	55%	NC was greater among men, unemployed, African Americans, and those with more drugs prescribed, higher levels of depression, and perceiving more barriers to following regimen.	
Frazier et al., (1994)[11]	Mail questionnaires	241 Functioning graft	Patient reports frequency of missed medications and reasons for missing.	50%	NC associated with depression, female sex, younger age, lower incomes, not married, and retransplanted.	

Table II. Contd

Reference	Research design	No. pts/ selection criteria	Measures of noncompliance	% Noncompliant	Factors associated with noncompliance	Clinical consequences of noncompliance
Sketris et al., (1994)[12]	Mail questionnaires	361 receiving CsA	Patient reports; 3 categories: compliant, somewhat compliant, NC	65%	NC associated with ↑ education, ↑ number of drugs prescribed, ↓ age, ↑ number of adverse effects, and ↑ number of rejection episodes.	
DeGeest et al., (1995)[13]	Descriptive, cross-sectional; interviews and questionnaires	148 ≥1yr after tx and no major clinical event; receiving CsA	Patient reports of compliance within last 12m	22%	Logistic regression predictors of NC: marital status (single), ↓ situational- operational knowledge, ↓ self-care agency, ↓ knowledge about medication administration, ↓ self-efficacy	The incidence of late acute rejection was significantly lower between those who complied (6%*vs* 24%, p = 0.003); 5-yr survival was significantly higher for compliers than noncompliers (99%*vs* 94%, p = 0.03).
Hillbrands et al., (1995)[14]	Prospective record reviews and interviews	127 Followed for first year after tx	Pill counts; NC = adherence to medication regimen <80% of the time	23% for CsA 13% for Aza 23% for prednisone	No consistent relationship between NC and demographic variables; compliance↑ after a rejection episode.	Patients who developed an acute rejection showed a worse degree of compliance with a higher incidence of underconsumption.
Siegal & Greenstein, (1997)[15]	Questionnaires; chart review and retrospective chart reviews	n = 519 subset = 397 receiving CsA	Patient reports of forgetting to take, deciding not to take, or adjusting the dose or frequency of CsA within last 4wk	18%	NC related to being away from home, ↑ time since tx, ↓ age, male sex, non-Caucasian race, belief that after tx symptoms will persist, belief that medications are not effective.	
Greenstein & Siegal, (1998)[16]	Questionnaires	n = 2500	Patient reports	22%	NC related to ↓ age, ↑ time since tx, having some college education, employed white collar occupation, LRD allografts, born outside the US, and those without diabetes mellitus	
Raiz et al.(1999)[17]	Questionnaire	n = 357; ≥1yr after tx	Patient reports	26%	Younger patients more likely to forget to take their medications; individuals who perceived less functioning (more limitations) related to pain, believed that chance controlled their health outcomes, and were bothered by any part of the transplant experience were more likely to forget their medications.	
Chisholm, et al. (2001)[18]	Refill records	IG = 12 CG = 12	Refill and medical records	IG = 25% CG = 68%	Patients who received clinical pharmacy services had better compliance than patients without these services.	IG = Did not have any rejection CG = 2 pts experienced a rejection.

a Included data from S_1 and S_2 reported by Rovelli et al., 1989.[6,7]

Aza = azathioprine; **CG** = control group; **CsA** = cyclosporin; **IG** = intervention group; **LRD** = living related donor; **NC** = noncompliant; **S** = study; **SES** = socioeconomic status; **tx** = transplant.

monly used methods include patient interviews, serum drug concentration measurements, pill counts, refill records and chart reviews. As expected, each method has limitations. In addition, the schedule of follow-up appears to influence compliance rates. For example, individuals in prospective trials generally have greater rates than those in retrospective trials or routine settings.[6-8]

Many of the studies suggest that transplant recipients who are married and Caucasians are more adherent to immunosuppressive therapy than their counterparts.[5,11,13] Medication nonadherence is also associated with depression, increased stress, taking numerous drugs per day, adverse effects attributed to immunosuppressive therapy, retransplantation, lack of confidence in prescribed medication, low self-efficacy, a low knowledge concerning health, lack of private insurance, and being of foreign descent (possibly due to a language barrier).[9-13,16]

Recipients who have had their transplanted organ(s) for a longer length of time also show an increased likelihood of nonadherence. This may be as a result of recipients becoming less attentive to their medication regimens as time passes.[15,16] Studies also indicate that younger adult transplant recipients have a lower adherence rate than older recipients.[6-8,11,12,15,16]

One study found that recipients who had living-related donors (LRDs) were less adherent than those who had cadaveric donors.[16] The investigators of the study commented that the recipients with grafts from LRDs may be less compliant as a consequence of the recipients' beliefs that their allografts are relatively histocompatible – thereby, diminishing the recipients' incentive to rigourously follow medication protocols.[16] After rejection, immunosuppressive adherence increases.[14]

Individuals of lower socioeconomic status (SES) were found to be less adherent than those of higher status.[6,7] Perhaps those with higher SES had higher education levels that led to increased adherence. However, data supporting this was not found. In fact, recipients with elementary school education were more adherent than those with college education.[12] It is important not to confuse education level with knowledge concerning medication; those who had greater knowledge about medication administration were found to be more adherent to therapy.[13]

Results concerning the influence of employment on medication adherence are conflicting. In 1993, Kiley and colleagues showed that transplant recipients who were employed were more adherent than those who were unemployed.[10] However, in 1998 Greenstein and colleagues demonstrated that recipients who were employed full or part-time and those who identified themselves as having white collar occupations were more likely to be nonadherent than their counterparts.[16] In the latter study, individuals who were more accustomed to providing leadership and making decisions in their occupations more frequently decided not to rigourously follow their immunosuppressive therapy regimens.[16]

Noncompliance is not only seen in renal transplant recipients. Studies indicate that noncompliance is seen in recipients of all types of solid-organ transplants. For example, Schweizer et al. reported noncompliance among heart and liver transplant recipients.[8] Lanza and Cooper associated clinical outcomes with noncompliance and found that 23% of deaths or loss of allograft function in heart transplant recipients were related to noncompliance.[19] Therefore, patients who have transplants that are life sustaining are also noncompliant to therapy.

Although the studies in table II list many factors associated with noncompliance, most of the investigators concluded that noncompliant behaviour is usually not predictable and this data should be used only as a guide to those who may be at greater risk for nonadherence. As a result of detrimental adverse events, emphasis should be placed on increasing medication adherence in all transplant recipients.

4. Factors Contributing to Immunosuppressive Nonadherence

Nonadherence with immunosuppressive regimens has been attributed to confusion concerning

Table III. Adverse effects of immunosuppressive medications

Drug	Adverse Effects
Azathioprine	>10%: fever, chills, nausea, vomiting, anorexia, diarrhoea, thrombocytopenia, leucopenia, anaemia, infection
	1-10%: rash, pancytopenia, hepatotoxicity
	<1%: hypotension, alopecia, maculopapular rash, apthous stomatitis, arthralgias (myalgias), rigours, retinopathy, dyspnea, rare hypersensitivity reactions, Raynaud's disease, pulmonary oedema
Cyclosporin	>10%: hypertension, hirsutism, hypomagnesaemia, hypokalaemia, gingival hypertrophy, tremor, hypercholesterolaemia, nephrotoxicity
	1-10%: seizure, headache, acne, abdominal discomfort, nausea, vomiting, cramps
	<1%: hypotension, tachycardia, flushing, hyperkalaemia, hyperuricaemia, pancreatitis, hepatotoxicity, myositis, paresthesias, respiratory distress, sinusitis, anaphylaxis, infection
Mycophenolate mofetil	>10%: pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, hypertension, tremor, insomnia, dizziness, acne rash, diarrhoea, constipation, nausea, dyspepsia, vomiting, oral monoliasis, anaemia, leucopenia, thrombocytopenia, hypochromic anaemia, leucocytosis, peripheral oedema, hypercholesterolaemia, hypophosphataemia, oedema, hypokalaemia, hyperkalaemia, hyperglycaemia, infection, dyspnea, cough, pharyngitis, bronchitis, pneumonia, haematuria, kidney tubular necrosis, urinary tract disorder
Prednisone	>10%: insomnia, nervousness
	1-10%: hirsutism, diabetes mellitus, cataracts, glaucoma, arthralgia, epistaxis
	<1%: oedema, hypertension, vertigo, seizures, psychoses, pseudotumour cerebri, headache, mood swings, delirium, hallucinations, euphoria, acne, skin atrophy, bruising, hyperpigmentation, Cushing's syndrome, pituitary-adrenal axis suppression, growth suppression, glucose tolerance, hypokalaemia, alkalosis, amenorrhoea, sodium and water retention, hyperglycaemia, peptic ulcer, nausea, vomiting, abdominal distention, ulcerative esophagitis, pancreatitis, muscle weakness, osteoporosis, fractures, muscle wasting, hypersensitivity reactions
Sirolimus	>20%: hypercholesterolaemia, hypertriglyceridaemia, hypertension, rash, acne, anaemia, arthralgia, diarrhoea, hypokalaemia, thrombocytopenia, leucopenia, fever
Tacrolimus	>10%: hypertension, peripheral oedema, headache, insomnia, pain, fever, pruritus, hypokalaemia, hyperkalaemia, hyperglycaemia, hypomagnesaemia, diarrhoea, nausea, anorexia, vomiting, abdominal pain, anaemia, leucocytosis, LFT abnormalities, ascites, tremors, paresthesias, back pain, weakness, pleural effusion, altelectasis, dyspnea, infection, nephrotoxicity
	1-10%: seizures, rash, hyperphosphotaemia, hyperuricaemia, pancreatitis, constipation, thrombocytopenia, myoclonus, dysuria, nocturia, oliguria, renal failure, urinary frequency, urinary incontinence, angina pectoris, abnormal ECG, hypotension, vasodilation, tachycardia
	<1%: hypertrophic cardiomyopathy, arthralgia, myalgia, haemolytic uraemic syndrome, anaphylaxis, expressive aphasia, photophobia, secondary malignancy, palpitations

ECG = electrocardiogram; **LFT** = liver function tests.

proper use, lack of appropriate instructions from practitioners, apathy, intentional failure to comply because of adverse effects or other reasons, and inability to purchase or take the medication properly for economic reasons.[4] In this section, a few of the most common reasons leading to a reduction in immunosuppressant adherence are discussed.

Noncompliance is associated with increased number of prescribed drugs.[10,20] Most transplant recipients require numerous drugs each day, and often, many of these are required long term. It is not unusual for transplant recipients to take more than eight different drugs per day, with some agents being administered multiple times per day. Therefore, it is not surprising that transplant recipients may get confused as to how to take their drugs properly. Furthermore, as a result of the limited strengths and dosages available, immunosuppressant regimens are complicated. Taking numerous capsules per day and varying doses of immunosuppressant therapy per day is common to achieve the proper degree of immunosuppression. For example, a recipient who is prescribed cyclosporin 150mg each morning and 175mg each evening has to take seven capsules of cyclosporin daily. Complicated regimens make adherence cumbersome, inconvenient and confusing. To prevent drug-related adverse effects, individuals may decrease compliance. Immunosuppressive therapy is associated with several adverse effects (see table III). Recipients who expected adverse effects or actually experienced adverse effects due to immunosuppres-

sive therapy had lower adherence rates.[12] No literature was found describing which adverse effects influence immunosuppressive therapy nonadherence the most.

Inadequate access to medication is a tremendous adherence barrier. In the US, Medicare is a major payer for outpatient immunosuppressive therapy. With immunosuppressant therapy typically costing greater than $US10 000 per year, it comes as no surprise that compliance may be limited by an individual's inability to purchase immunosuppressant agents. Although Medicare pays for 80% of immunosuppressant therapy, individuals may not be able to pay the other 20% of the cost which typically ranges between $US150 and $US300 per month. Raiz and colleagues suggest that 20% of recipients had difficulty paying for immunosuppressant therapy.[17] In 1999, Kory reported that 53% of transplant recipients spent at least $US50 or more per month out-of-pocket on medications, 11% spent greater than $US300 per month out-of-pocket, and only 6% reported no out-of pocket expenses.[21] If an individual does not have drugs because of a lack of purchasing power, adherence is not a possibility. Access to immunosuppressive therapy because of expense can be a serious barrier to therapy. Lack of private insurance was found to decrease adherence to immunosuppressive therapy in certain populations.[9] Table IV lists other contributors to medication nonadherence.[4,22-25]

5. Enhancing Adherence to Immunosuppressive Therapy

Factors influencing patients' adherence to immunosuppressive can be sorted in four major categories including motivation, knowledge, skills and access (see figure 1).

Table IV. Factors that affect medication adherence. Adapted from references[4,22-25]

Factors that reduce medication adherence	Factors that promote medication adherence
Lack of symptoms or complications	Developing symptoms or complications
Lack of knowledge about key components of health and therapy	Knowledge about medications and illness
Chronic illness or disease	Acute illness
Patients who are depressed or have other illnesses that affect psychological and cognitive senses	Patients who are not depressed or have other illnesses that affect psychological and cognitive senses
Negative expectations or attitudes toward therapy	Positive expectations or attitudes toward therapy
No instructions given	Written and verbal instructions
Lack of comprehension of instructions (drug therapy)	Comprehension of instructions (drug therapy)
Treatment requires significant behaviour changes	Convenience of therapy
Complex regimens	Simple regimens
Formulations that are bad tasting or difficult to swallow	Palatable formulations or formulations that are easily swallowed
Unknowledgeable and undependable caregivers (e.g. parents in the case of paediatric patients)	Knowledgeable and dependable caregivers (e.g. parents in the case of paediatric patients)
Medication takes a long time before providing symptomatic relief, or provides no relief	Medication quickly provides symptomatic relief
Actual or perceived unpleasant adverse effects	Lack of actual or perceived unpleasant adverse effects
Lack of communication and unsatisfactory relationship with healthcare practitioners	Good communication and satisfactory relationship with healthcare practitioners
Lack of patient participation in devising treatment plan	Patient participation in devising treatment plan
Lack of confidence in the healthcare practitioners	Confidence in the healthcare practitioners
Lack of social support	Presence of positive role models and support of family members and friends
Presence of cognitive and physical disabilities	Free of cognitive and physical disabilities
Failure to recognise the need for medication	Recognises need for medication
Health is a low priority	Health is a high priority
Inadequate access to care (e.g. inadequate resources to pay for medication)	Adequate access to care (e.g. adequate resources to pay for medications)

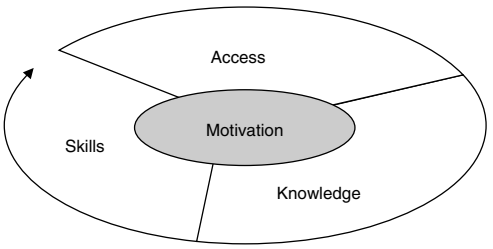

Fig. 1. Factors influencing medication adherence. Patient motivation is the core of the model and represents the driving force. Motivation incorporates the beliefs, values, attitudes and willingness toward adherence of the patient. The ability of the patient to obtain access to care, knowledge (comprehension) and skills to follow therapy influences medication adherence.

Motivation incorporates patient's beliefs, values, attitudes and willingness toward adherence. Since there is a positive correlation between medication nonadherence before transplant and nonadherence after transplant,[26,27] it is important to ascertain the beliefs of a recipient concerning therapy and assess adherence to therapy both pre- and post-transplant. Furthermore, the importance of maintaining the newly transplanted organ and the great opportunity to enhance quality of life by adequately supporting the transplanted organ should be reinforced.

Modifying treatment recommendations to reflect patient preferences can enhance adherence. Something as simple as the dosage form can make a significant difference in adherence. For example, most immunosuppressants come in both liquid and capsule formulations. Since liquid formulations may be unpleasant to taste, most adult recipients who are capable of swallowing prefer capsules.[12] Since many children under 12 years of age have difficulty swallowing capsules, liquid formulations may be preferred in this population. Therefore, including recipient preferences when designing drug therapy is important. Having recipient participation in designing therapy also helps to promote self-efficacy.

Having adequate knowledge is essential for both the healthcare practitioner and patient. Transplant recipients better adhere to therapy when their clinicians are familiar with adherence strategies. For example, transplant recipients who have a clinical pharmacist involved in their care better adhere to immunosuppressive therapy than recipients who do not have clinical pharmacist involvement.[18] Additionally, healthcare professionals need to empower transplant recipients by providing them with adequate information. Since recipients have different learning abilities, it is important to give recipients information that is tailored to their education level to facilitate understanding. Multiple techniques should be used to educate recipients, realising that one method may not be effective for all individuals. Verbal and written instructions are commonly used to inform patients as to how to take their therapy. However, other methods of instruction such as videotapes, computer-assisted programmes, the Internet, and interactive videoconferencing can also be used to deliver information to patients in an effective manner. Table III lists other factors that may enhance the adherence to therapy of transplant recipients.[4,22-25]

6. Conclusions

Nonadherence to drug therapy is the most significant problem facing medical practice today.[28] Studies indicate that increased morbidity and mortality are possible consequences of immunosuppressant nonadherence. Therefore, medication adherence is a critical issue in transplantation.

Nonadherence with immunosuppressive therapy is frequent, ranging from 2% to 68%, and is seen among recipients of all types of solid-organ transplants. Possible reasons for this wide range include differences in methodology used in the studies measuring adherence. For example, the schedule of follow-up (prospective versus retrospective study) and the type of measurement used to assess compliance (serum drug concentration monitoring, patient interviews, refill records, etc.) influence rates with prospective trials and patient interviews report higher compliance rates.

This manuscript presents several issues concerning immunosuppressant adherence including a literature review of factors associated with nonad-

herence and the consequences of nonadherence. To receive a precious gift, such as an organ, and to lose it as a result of nonadherence is a tragedy. It is imperative to facilitate immunosuppressant adherence to all transplant recipients.

Acknowledgements

This work was supported by a grant from the Carlos and Marguerite Mason Trust Fund.

References

1. Sackett DL, Haynes RB. Compliance with therapeutic regimens. Baltimore (MD): Johns Hopkins University Press, 1976
2. Meichenbaum D, Turk DC. Treatment adherence: terminology, incidence, and conceptualization. In: Facilitating treatment adherence: practitioner's guidebook. New York: Plenum Press, 1987:19-40
3. Rudd P. In search of the gold standard for compliance measurement. Arch Intern Med 1979; 139: 627-8
4. Stewart RB and Caranasos GJ. Medication compliance in the elderly. Med Clin North Am 1989; 73: 1551-63
5. Didlake RH, Dreyfus K, Kerman RH, et al. Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants. Transplant Proc 1988; 20: 63-9
6. Rovelli M, Palmeri D, Vossler E, et al. Noncompliance in organ transplant recipients. Transplant Proc 1989; 21: 833-4
7. Rovelli M, Palmeri D, Vossler E, et al. Noncompliance in renal transplant recipients: evaluation by socioeconomic groups. Transplant Proc 1989; 21: 3979-81
8. Schweizer RT, Rovelli M, Pameri D, et al. Noncompliance in organ transplant recipients. Transplantation 1990; 49: 374-7
9. Butkus DE, Meydrech EF, Raju SS. Racial differences in the survival of cadaveric renal allografts: overriding effects of HLA matching socioeconomic factors. N Engl J Med 1992; 327: 840-5
10. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. Transplantation 1993; 55: 51-6
11. Frazier P, Davis-Ali S, Dahl K. Correlates of noncompliance among renal transplant recipients. Clin Transpl 1994; 8: 550-7
12. Sketris I, Waite N, Grober K, et al. Factors affecting compliance with cyclosporine in adult renal transplant patients. Transplant Proc 1994; 26: 2538-41
13. DeGeest S, Borgermans L, Gemoets H, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995; 59: 340-7
14. Hilbrands LB, Hoitsma AJ, Koene RAP. Medication compliance after renal transplantation. Transplantation 1995; 60: 914-20
15. Siegal BR, Greenstein SM. Postrenal transplant compliance from the perspective of African-Americans, Hispanic-Americans, Anglo-Americans. Adv Ren Replace Ther 1997; 4: 46-54
16. Greenstein S, Siegal B. Compliance and noncompliance in patients with a functioning renal transplant: a multicenter study. Transplantation 1998; 66: 1718-26
17. Raiz LR, Kilty K, Henry ML, et al. Medication compliance following renal transplantation. Transplantation 1999; 68: 51-5
18. Chisholm M, Mulloy L, Jagadeesan M, et al. Impact of clinical pharmacy services on renal transplant patients compliance with immunosuppressive medications. Clin Transplant 2001; 15: 330-6
19. Lanza RP, Cooper DKC. In: Heart transplantation: the present status of orthotopic and heterotopic heart transplantation. Boston (MA): MTP Press, 1984:300
20. Murphy J, Coster G. Issues in Patient Compliance. Drugs 1997; 54 (6): 797-800
21. Kory L. Non-adherence to immunosuppressive medications: a pilot survey of members of the transplant recipients international organization. Transplant Proc 1999; 31: 14S-5S
22. Becker MH, Maiman LA. Strategies for enhancing patient compliance. J Community Health 1980; 6: 113-35
23. Nichols-English G, Poirier S. Optimizing adherence to pharmaceutical care plans. Am Pharm 2000; 40: 475-85
24. Bush PT, Lanotti RJ. A children's health belief model. Med Care 1990; 28: 69-86
25. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Arch Intern Med 2000; 60: 2101-7
26. Douglas S, Blixen C, Bartucci MR. Relationship between pretransplant noncompliance and posttransplant outcomes in renal transplant recipients. J Transpl Coord 1996; 5: 53-8
27. Ramos El, Kasiske BL, Alexander SR, et al. The evaluation of candidates for renal transplantation. Transplantation 1994; 57: 490-7
28. Eraker SA, Kirscht JP, Becker MH. Understanding and improving patient compliance. Ann Intern Med 1984; 199: 258-68

Correspondence and offprints: Dr *Marie A. Chisholm*, Department of Clinical and Administrative Sciences, University of Georgia College of Pharmacy and Department of Medicine, Medical College of Georgia, CJ-1020, Augusta, 30912-2450, USA.
E-mail: mchishol@mail.mcg.edu