ORIGINAL ARTICLE

Medication Compliance Among Renal Transplant Patients: A Hospital Kuala Lumpur Experience

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Summary

This survey aims to identify prevalence, reasons and predictors of noncompliance among renal transplant patients followed up in Hospital Kuala Lumpur (HKL). All adult renal transplant patients who were at least 6 months post transplant were recruited from 10/2001 till 5/2002. Patients who consented were interviewed by a medical doctor or research assistant based on questionnaire. Noncompliers were defined as those who missed or self adjusted any dose of immunosuppressant within the preceding 4 weeks. Inter-rater agreement was assessed prior by Kappa (K) scores and they were acceptable. Out of 304 patients, 246 patients volunteered; of whom 144 (58.5%) were males. Twenty-one (9.3%) were noncompliers. Reasons for noncompliance included forgetfulness (n=8), financial constraints (n=1), fear of rejection (n=1), side effects (n=9), decision not to take (n=6), difficulty in breaking medication into correct dosages (n=1). Significant predictors of noncompliance were longer duration of transplant, noncompliance to other drugs, regular use of nonprescription drugs; the lack of symptoms of fat facial cheeks and infection. Surveillance for noncompliance should not be relaxed as its predictors are diverse and persistent, especially in those who are at high risks.

Key Words: Compliance, Renal transplant

Introduction

Long term successful outcome after renal transplantation necessitates life long treatment with immunosuppressants. Noncompliance is a significant if not the single most important contributing factor in transplant rejection[1-5]. In a landmark study, noncompliance with immunosuppressants was the third leading cause of graft loss, after rejection and systemic infection[6]. According to the Malaysian Dialysis and Transplant Registry[7], 65% of graft failures that occurred in 1999 were due to rejection. The actual impact of noncompliance on chronic rejection remains unknown. Noncompliance in this paper is defined as the patient admitting during the interview to having missed or self adjusted any dose of immunosuppressant (including prednisolone, azathioprine, mycophenolate mofetil [MMF], cyclosporine microemulsion, tacrolimus) over the preceding 4 weeks[8]. In this cross-sectional survey, we investigated the prevalence, reasons and predictors of noncompliance.

Materials and Methods

Study population and procedure

A literature search was done and a two-page survey form was designed (Appendix 1). All adult patients with a functioning renal transplant for at least six months, followed up in the Nephrology clinic, Hospital Kuala Lumpur (HKL) were eligible for the study. The survey was carried out over 8 months from October 2001 to May, 2002. Every patient was interviewed by

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either the author (LWJ) or a research assistant (RA) from the Clinical Research Centre of HKL (who was off uniform), based on a set of questions. There were 2 research assistants conducting most of this survey. Arbitrarily, 5 patients were randomly chosen to be interviewed by 2 RAs in turn. The responses collected from both interviewers were compared to assess inter-rater agreement. Such comparison were also done between LWJ and one of the RAs on 4 patients. The latest trough cyclosporine levels using TDX Cyclosporine monoclonal whole blood reagent by Abbott®, were recorded. Normal cyclosporin trough level is between 100 – 250 ng/ml. Similarly, the latest trough tacrolimus levels using IMx tacrolimus II by Abbott®, were recorded. Normal tacrolimus trough levels are 5 – 15 ng/ml.

Variables and measurement

Demographic and transplant data, medication regimen (immunosuppressants and others), cost of immunosuppressants, health beliefs concerning immunosuppressants, immunosuppressant related side effects and frequency, reasons of noncompliance, duration and memories of dialysis, history of late acute or chronic rejection were elicited from the patient and case notes. Concerning memories of dialysis, one question was asked : How often did dialysis get in the way of the things you liked to do. There were four possible answers for the patient to choose from. Answer one was "never interfered" and answer four was "always interfered".

Four statements on health beliefs concerning medication were assessed : (i) the need to take the drugs even if the kidney is well; (ii) drugs should never be delayed; (iii) immunosuppressants stay active in the body for less than 24 hours; (iv) I need the drugs to keep the kidney. Patients could respond either yes, no or don't know. All the statements were true.

Cyclosporine trough level of >25 ng/ml[6] or > 30 ng/ml[9] was used to define compliance. In this study, latest cyclosporin and tacrolimus trough levels of > 25 ng/ml and >1 ng/ml respectively were used arbitrarily to define compliance.

Late acute rejection is defined as an episode of declining urine output with rapidly rising serum creatinine occurring more than 3 months post renal transplant, in the absence of other causes of graft dysfunction and where anti-rejection therapy was instituted.

Chronic rejection is defined clinically as gradual increase in serum creatinine over months or years in the absence of other causes of graft dysfunction, with worsening proteinuria and hypertension. Data were analysed using Medcalc for Windows®. The statistical tests applied in this study were the Chi-square test, Mann-Whitney test and student t test. Inter-rater agreement between two interviewers was quantified by K (Table I).

Table I: Strength of agreement according to Kappa (K) values

Value of K	Strength of agreement
<0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very good

Results

The calculated Kappa values were 0.77 and 0.9 between 2 RAs and between LWJ and one of the RAs respectively.

There were 304 patients with a functioning graft of at least 6 months, regularly followed up in HKL. Fifty-three patients were not contactable while 5 patients refused to participate. Of the 246 patients who consented for the interview, 21 (9.3%) patients were found to be noncompliers. Reasons for noncompliance were medication side effects (n=9), forgetfulness (n=8), decision not to take (n=6), financial constraints (n=1), difficulty in breaking medication into correct dosages (n=1), and fear of rejection (n=1). The three most common side effects post transplant were hypertension (n=207) (84.5%), fat facial cheeks (n=190) (77.2.%) and hirsutism (n=175) (71.1%). All patients who were on cyclosporin microemulsion had trough levels of > 25 ng/ml except for 1 patient who was a case of squamous cell carcinoma positive for hepatitis B and C, intended to have a low cyclosporin level. All patients who are on tacrolimus had trough levels of > 1 ng/ml.

A total of 62 (25.2%) patients used nonprescription medications regularly, namely Chinese herbs (e.g. linzhi and ginseng) and direct-selling health products (e.g. EXCEL, extracts from aloe vera, grains and Almansor tea leaves).

One Hundred and ten responders were on cyclosporine microemulsion, azathioprine and prednisolone. The majority of the living related transplants were done at Hospital Kuala Lumpur (except for 2 in Taiwan, 2 in Singapore, 2 in Australia and 1 in India). Most living unrelated transplants were done in India (except for 1 in Pakistan). All commercial cadaveric transplants were done in China. Those who had renal transplant done in Hospital Kuala Lumpur do not pay for immunosuppressants. Transplants done overseas with at least 1 year duration were entitled to free cyclosporine microemulsion from the Ministry of Health of Malaysia. Twenty responders paid for their immunosuppressants e.g. cyclosporine microemulsion or tacrolimus and/or MMF. The monthly costs of cyclosporine (300 mg per day) microemulsion, tacrolimus (12 mg per day) and MMF (2g per day) were RM1200/-, RM3120/- and RM1700/- respectively. Significant predictors for noncompliance to immunosuppressants were the longer duration of transplant, regular usage of nonprescription medication, noncompliance to other medication, lack of symptoms of fat facial cheeks and infection. (Table II, III, IV, V,)

Table II: Comparison between compliers and noncompliers in terms of demography

Variable	Compliers (n = 225)	Noncompliers (n = 21)	p
Age in years (Median [95% CI])	42(41-44)	46(41-52)	0.14
Sex		0.41	
Male	134	10	
Female	91	11	
Race			0.45
Malay	55	3	
Chinese	143	17	
Indian	24	1	
Others	3	0	
Marital Status			0.31
Married	157	14	
Single	66	6	
Divorced	2	1	
Income (RM)			0.65
<1,000	75	5	
1 - 2,000	81	10	
2 - 3,000	32	2	
>3,000	37	4	
Education			0.30
None	7	0	
Primary	49	3	
Secondary	121	10	
Tertiary	48	8	
Donor Type			0.15
Commercial cadaveric	54	4	
Living related	106	10	
Living unrelated	38	7	
Local cadaveric	25	0	
Spousal	2	0	

Variable	Compliers (n = 225)	Noncompliers (n = 21)	p
Diabetes Mellitus			0.79
Nondiabetic	194	18	
Diabetic	31	3	
Number of Transplant			
1	211	21	0.50
2	7	0	
3	7	0	
Cost of Immunosuppressants			0.87
Paying	18	2	
Free	207	19	
Duration of Transplant in months (Median [95% CI])	86 (74-93)	121 (98-158)	0.01
Duration of dialysis in months (Mean ± SD)	30.28 ± 47.77	16.38 ± 17.34	0.18
Transplant place			0.27
China	55	4	
India	38	7	
Kuala Lumpur	125	10	
Others	7	0	

Table III: Comparison between compliers and noncompliers in terms of medication regimen, noncompliance to other drugs, history of rejection, missed clinics

Variable	Compliers (n=225)	Noncompliers (n=21)	p
No. of Tablets (Median [95% CI])	12 (11.8-14)	11(8-15)	0.19
No. of Medication (Median [95% CI])	5 (5-5)	5 (4-7)	0.89
Frequency of Medication (Mean ± SD)	2.66 ± 0.99	2.90 ± 1.45	0.30
Regular usage of nonprescription medication			0.03
Y	52	10	
N	173	11	
Noncompliance to other drugs (e.g. antihypertensive)			0.02
Y	51	10	
N	174	11	
Late acute / chronic rejection			0.42
Y	42	6	
N	183	15	
Missed Clinics			0.75
Y	9	0	
N	216	21	

Table IV: Comparison between compliers and noncompliers in terms of health beliefs

Variable	Compliers (n= 225)	Noncompliers (n= 21)	p
Memories of dialysis			0.81
1 (Never interfered)	20	1	
2	17	1	
3	37	4	
4 (Always interfered)	151	15	
Health belief (i)			0.68
Y	217	21	
N	1	0	
Don't know	7	0	
Health belief (ii)			0.88
Y	217	20	
N	1	0	
Don't know	7	1	
Health belief (iii)			0.06
Y	203	18	
N	0	2	
Don't know	22	1	
Health belief (iv)			0.14
Y	224	21	
N	0	0	
Don't know	1	0	

Table V: Comparison between compliers and noncompliers in terms of side effects

Side effects related to immunosuppressants	Compliers (n=225)	Noncompliers (n=21)	p
Leg oedema			0.92
Y	89	8	
N	136	13	
Hypertension			0.88
Y	190	17	
N	35	4	
Weak muscles			0.89
Y	94	9	
N	131	12	
Nervous / sad			0.53
Y	86	6	
N	139	15	
Hirsutism			0.22
Y	163	12	
N	62	9	
Gum hypertrophy			0.55
Y	107	8	
N	118	13	

Side effects related to immunosuppressants	Compliers (n=225)	Noncompliers (n=21)	p
Fat facial cheeks			0.04
Y	178	12	
N	47	9	
Acne			0.43
Y	101	7	
N	124	14	
Weight gain			0.05
Y	159	10	
N	66	11	
Low total white count			0.81
Y	19	2	
N	206	19	
Infection			0.03
Y	109	3	
N	116	18	

Discussion

The response rate of 80.9% in this survey is considered good compared to other surveys which reported 56%[8] and 73%[9] response rates respectively. The K values represents good agreement between interviewers. The rate of noncompliance in this study was 9.3%. Kiley[10] found a high incidence of 53% of noncompliance to immunosuppressant therapy. Some studies[6, 11] however quoted noncompliance rates of < 5%. Such variation may be influenced by the different methods of measurement and definition of noncompliance. Some researchers used mail surveys or interviews which were based on self reporting. Others used case record reviews[10, 11, 12, 13] (either prospective or retrospective). It is therefore difficult to compare noncompliance rates since there is no standardised criteria to measure noncompliance. The criteria chosen in this study is modeled from the recent largest study on noncompliance to immunosuppressants[8].

The two most common reasons for noncompliance were side effects (n= 9) and forgetfulness (n=8). Several studies[6, 9, 11, 12, 14, 15] have shown that medication side effects lead to noncompliance. Studies[8] have shown that patients suffering from infection are more likely to noncomply. However, contrary to the literature, this study found that those who noncomply reported having significantly less symptoms of fat facial cheeks and infection. This may reflect an effect rather than a cause of noncompliance. Noncompliance can reduce the occurrence of such side effects if it is practiced consistently over time. Considering that those who noncomply tend to have longer duration of transplant and usage of additional nonprescription medication as health supplements, the accumulative effects may translate into a lower rate of symptomatology.

Dosing frequency was found to contribute to noncompliance[16]. Forgetfulness, being one of the common reasons cited for noncompliance[9, 14], can be overcome if daily dosing of immunosuppressants is available.

Regular usage of nonprescription medication is common amongst the local healthy population. However, the literature on the usage patterns among transplant patients remains scanty. Health supplements from direct selling and traditional herbal medication are the main types. Such behaviour predicts noncompliance where patients may falsely assume a higher efficacy of "supplementary" medication compared to the conventional immunosuppressants which have their inherent side effect profile.

We found longer duration of transplant was predictive of noncompliance. This is in keeping with other authors' findings [1, 8, 9, 17]. Dew et al [17] found increasing difficulties with the immunosuppressant regime as reported by the patients' themselves over time. This is contrary to the expectation that patients should have a hard time coping with all new requirements in the early post transplant period (therefore less compliant) and subsequently getting used to the routine (therefore favours compliance). Longer time since transplant may predispose patients to become less attentive to medication regimen as time passes and their grafts are retained.

Costs of medication can impose tremendous financial burden on transplant patients. Raiz et al [3] suggested that 20% of patients had difficulty paying for immunosuppressants. Chisholm et al [2] in a small study found that patients who received their immunosuppressants free of charge were gradually compliant within their first year of treatment. However, compliance tended to reduce over time. Drug cost alone therefore does not explain noncompliance behaviour.

It was found in Greenstein's study [8] that patients were more likely to comply if they believed that (i) they need to take the drugs even if the kidney is well, (ii) drugs should never be delayed and (iii) immunosuppressants stay active in the body for less than 24 hours. It was postulated that these variables reflect patient's attitudes, understanding and practices needed to maintain long term health. Our findings showed that majority of the patients answered correctly belief (i), (ii) and (iv) among >96% of all responders. Question on belief (iii) exposed the ignorance of the duration of action of immunosuppressants in some patients (only 89.8% of patients answered correctly).

Patient education on the side effects of immunosuppressant can help to reduce misconceptions but unfortunately, most of these side effects are not avoidable. Drug interactions between immunosuppressants and other nonprescription drugs should be emphasized to avoid toxicities.

Further research is needed to identify ways to accurately measure compliance. The reduction of side effect profile of immunosuppressants will definitely make a huge impact on compliance amongst transplant recipients. Predictors for noncompliance once identified should be carefully tested in long term studies to ascertain their impact on graft survival.

Conclusion

Noncompliance is known to be an important cause of late graft failure. 9.3% of patients were found to be noncompliant. Side effects and forgetfulness were the two most commonly cited reasons for noncompliance. Significant predictors for noncompliance were the lack of symptoms of fat facial cheeks and infection, regular use of nonprescription drugs, longer duration of transplant and noncompliance to other drugs. Surveillance for noncompliance should not be relaxed as its predictors are diverse and persistent, especially in high risk patients.

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Appendix 1 **Survey form**

Date of Survey : _____

Name : _____ Age : ___ Sex : M / F District : KL/_____

Occupation : _____ Race : M / C / I / Others : ___ Marital Status : S / M / Divorced

Income (Family or self):☐: < $ 1000, ☐: $1000 - 2000, ☐: $2000 - 3000, ☐: >$3000

Level of Education: ☐: None ☐: Primary ☐: Secondary ☐: Tertiary

Diabetes : Y / N **Hypertension : Y / N**

Medication Data:

Drugs as in case notes								
Dosage								
Frequency per day								
Drugs according to pt.								
Dosage								
Frequency per day								
***Degree of compliance (self reporting)**								
****Reason(s) of noncompliance if M / S**								

***Degree of compliance**: NM / M / Self-adjusting (S) for each immunosuppressants, antihypertensives and others and reason(s) for noncompliance for each drug using the codes below.
(Compliance - never missed " NM" over the last 4 weeks. Noncompliance - missed "M" or self-adjusting "S" over the last 4 weeks)

****If M or S in the above boxes, state reason(s) for noncompliance according to code below:**

1. Forgetfulness.
2. Financial constraints.
3. Fear of rejection.
4. Ran out of supply.
5. Worried about side effects.
6. Decides not to take.
7. Others._____

Total no. of medications (including immunosuppressants, antihypertensives etc.) : _____

Dosing frequency(s) per day according to patient's schedule_____

Number of tablets per day _____.

Cost of immunosuppressants : (If paying, to indicate source_____/ Free).

Regular usage of nonprescription medications eg. Traditional / herbal / 'health' products .

Y / N If Y, list out type(s) and frequency(s) _____

_____

Missed clinic appointment(s) in the last 1 year : Y / N .

If yes, record number ____.

Duration on dialysis : _____months.

Memories of dialysis:
How often did dialysis get in the way of the things you liked to do?
☐ 1 (Never interfered) ☐ 2 ☐3 ☐ 4 (Always Interfered)

Beliefs concerning medication:

☐ Need to take the drugs even if the kidney is well.....Y / N / Don't know

☐ Drugs should never be delayed..... Y / N / Don't know

☐ Immunosuppressants stay in the body for < 24 hours.....Y / N / Don't know

☐ I need the drugs (immunosuppressants) to keep my kidney....Y / N / Don't know

Post Transplant Symptoms: (patient to report)

Posttx symptoms	Y / N	If yes, frequency of symptoms 1(<1/week) to 5(everyday)	Symptoms attributed to post transplant medication 1(complete disagree) to 5 (complete agree)
Swollen ankles		1 2 3 4 5	1 2 3 4 5
Weak muscles		1 2 3 4 5	1 2 3 4 5
Nervous / Sad		1 2 3 4 5	1 2 3 4 5
Hypertension		Nil	1 2 3 4 5
Hirsutism		Nil	1 2 3 4 5
Gum hypertrophy		Nil	1 2 3 4 5
Fat facial cheeks		Nil	1 2 3 4 5
Acne		Nil	1 2 3 4 5
Weight gain		Nil	1 2 3 4 5
		Frequency : 1(< 1 per year) to 6 (> 1 per month)	
Low white cell count		1 2 3 4 5 6	1 2 3 4 5
Infection		1 2 3 4 5 6	1 2 3 4 5

Transplant characteristics:
☐Commercial Cadaveric ☐Commercial Living ☐Living Related ☐Cadaveric ☐Living Emotional
Date of transplant : ___ No. of transplant : _____
Duration of transplant till NOW: _____months (only full month is counted)
Last known Cyclosporine/FK506 level : _____, date : _____
History of rejection Y / N If yes : list out episode(s)
1. Date _____Late Acute / Chronic, biopsy Y / N, creatinine normalised Y / N
2. Date _____Late Acute / Chronic, biopsy Y / N, creatinine normalised Y / N