Noncompliance With Immunnosuppressive Medications After Renal Transplantation

Ahad J. Ghods, Dariush Nasrollahzadeh

Noncompliance with immunosuppressive medications in renal transplant recipients results in higher rate of acute rejection episodes, allograft dysfunction, graft loss and patient death. We studied incidence and risk factors of medications noncompliance in 286 renal transplant recipients who were consecutively seen in our renal transplant clinic between February and April 2002. One hundred and seventy were male, 116 female. Their age ranged from 12 to 70 years (mean 39.1 ± 11.6). The length of time since the date of transplantation ranged from 5 to 231 months (mean 76.7 ± 53.5). The results of study showed that 70 patients (24.5%) to be noncompliant (7.7% noncompliant minor and 16.8% noncompliant major). The time since the date of transplanation was a significant risk factor in both noncompliant minor and major groups (P<0.001 and P<0.001). The other risk factors associated with major noncompliance was young age (P<0.001), lower level of education (P<0.01), lower socioeconomic class (P<0.05), addiction and psychiatric disorders (P<0.05). Transplant recipients with major noncompliance also had more acute rejection episodes (P<0.001) and allograft dysfunction (P<0.01). We conclude that noncompliance with immunosuppressive medications is very common in renal transplant recipients and it results to significant acute rejection episodes and allograft failure.

Keywords: *Immunosuppression; Renal allograft failure; renal transplantation; noncompliance*

Noncompliance with immunosuppressive medications is frequent among renal transplant recipients and has been reported to be the third leading cause of renal allograft loss, after rejection and systemic infection [1].

The reported incidence of noncompliance in renal transplant recipeients varies from less than 5% to more than 50% depending on the methods of measurements, definitions that were used for noncompliance and the characteristics of the patient population that were studied [2-3].

Most of the reports regarding noncompliance with immunosuppressive medications after renal transplantation are from developed countries. The results of these studies are being used by some transplant clinicians in order to increase

Transplantation Unit, Hashemi Nejad Kidney Hospital, Iran University of Medical Sciences, Tehran , Iran

***Acknowledgements**: I wish to gratefully acknowledge the efforts of P. Khosravani in collection of data and the sincere assistance of Leila Lak in preparation of manuscript.*

***Address reprint requests to**: Ahad J. Ghods, MD, FACP, President, Iranian Society of Nephrology, Hashemi Nejad Hospital, Vanak Square Tehran 19396, Iran. **Fax**: 98-21-2006561; **Tel**: 98-21-2009988; **E-mail**: ghods@iums.ac.ir*

Experimental and Clinical Transplantation (2003) 1: 39-47

medication compliance and to improve transplantation outcomes. The purpose of present study was to investigate the incidence and risk factors of noncompliance in our renal transplant recipients as an example for transplant population of developing countries in our region.

Patients and Methods

The study population consisted of 286 renal transplant recipients who were consecutively seen in renal transplant clinic during three mouths period between February and April 2002. All patients were interviewed during a private conversation by transplant physician or transplant coordinator and a questionnaire was completed for each patient. Their clinic records were reviewed. Data were analyzed and statistical test were employed.

The population characteristics of these 286 renal transplant recipients were as follows: One hundred and seventy patients were male, 116 female. Their ages ranged from 12 to 70 years. The mean age was 39.1±11.6 years. Two hundred and nine transplants were from living unrelated, 76 living related and only one transplant was from cadaveric donor. Twenty-four patients had retransplantation. The time since the date of transplantation ranged from 5 to 231 months (mean 76.7±53.5 months). More than 50% of patients had high school or university training. One hundred eighteen patients were from low, 95 from middle and 73 were from high socioeconomic class. Our definitions for these socioeconomic classes has previously been published [4]. Fourteen patients were heavy smokers or opiate addicts and 15 patients had some type of psychiatric disorders. According to patients clinic records in 182 patients there were no history of acute rejection episode. But history of one, two and three acute rejection episodes were present in 72, 27 and 5 patients respectively. The majority (71.7%) of transplant recipients had excellent allograft function with serum creatinine of less than 2 mg/dl. Two hundred and seventy four (95.8%) of transplant recipients were on cyclosporine and 97 (33.9%) were also receiving mycophenolate mofetil. Twelve patients were only on azathioprine and prednisone. We used following definitions for compliance and noncompliance in this study : Patients who did not miss any drug dose or they missed less than 3 doses per month were considered compliant. Those who missed 3 or more nonconsecutive doses per month were categorized as noncompliance-minor. Patients who missed 3 or more consecutive doses per month also those who stopped taking their medications for days, weeks or months were defined noncompliance-major.

Results

The results showed that 70 of 286 renal transplant recipients (24.5%) to be noncompliant with immunosuppressive medications. Twenty-two (7.7%) were noncompliant minor and 48 (16.8%) were noncompliant major. In Table 1, different variables in compliant and non-compliant renal transplant recipients have been compared. The time since the date of transplantation was significantly longer in both noncompliant-minor and major groups as compared with compliant renal transplant recipients ($P<0.001$). Younger age ($P<0.001$), low level of education ($P<0.01$), lower socioeconomic class ($P<0.05$), heavy smoking, opiate addiction and psychiatric disorders ($P<0.05$) were significantly more common in noncompliant

major renal transplant recipients as compared with compliant group. Gender, marital status, sources of renal allografts, retransplantation and immunosuppressive regimens showed no significant impact on noncompliance. As was expected, acute rejection episodes and advanced allograft dysfunction were also significantly more common (P<0.001 and P<0.01) in noncompliant major renal transplant recipients.

Discussion

The reported incidence of noncompliance with immunosuppressive medications in renal transplant recipients varies from less than 5% to more than 50%. This considerable variation in different studies is due to:

1- The discrepancy in arbitrary definitions that were used for noncompliance

2- Incomparable methods of measurements and

3- Dissimilarity in patient populations that were studied.

Uehling DT, et al. in 1976 defined noncompliance as major lapses when patients stopped medication for more than 3 weeks and minor lapses when medications was stopped for less than 3 weeks. The incidence of major lapses was 4% and minor lapses slightly higher [2]. In the study by Didlake RH, et al. major clinical noncompliance was defined by serum cyclosporine level of less than 25ng/mL and graft loss, minor clinical noncompliance by serum cyclosporine level of less than 25 ng/mL and rejection episode. The subclinical noncompliance was used for patients who missed doses of immunosuppressive medications

Table 1. Comparison of different variables in compliant and noncompliant renal transplant (Tx) recipients

Variables	Compliant N=216	Noncompliant-minor N=22	Noncompliant-major N=48
1. Age (years)	39.8±11.5	39.4 ±11.8	35.5 ±10.8 P<0.001
2. Sex (M / F)	130/86	11/11	29/19
3. Married/Single	172/44	17/5	38/10
4. LURD/LRD/CAD*	157/58/1	14/8/0	38/10/0
5. First Tx/Second Tx	198/18	20/2	44/4
6. Time Since Tx (months)	73.2±52.2	83.2±51.4 P<0.001	96.6±65.4 P<0.001
7. Education (low/high)	99/117	9/13	30/18 P<0.01
8. Economic class (low/middle/high)	82/69/65	8/8/6	28/18/2 P<0.05
9. Addiction /Psych	8/8	0/2	6/5 P<0.05
10. No. Acute Rejection	92	4	45
11. Allograft Dysfunction (serum creat. >5.0 mg/dl)	17	0	10 P<0.01
12. Immunosuppressives			
(CsA-AzA-Pred)	138	10	29
(CsA-MMF-Pred)	72	9	16
(AzA-Pred)	6	3	3

* Living unrelated donor/Living related donor/Cadaveric

without appearance of graft rejection or graft loss. The incidence of noncompliance with immunosuppressive medications in these three groups reported 2.8%, 1.9% and 15.7% respectively [1]. Kiley DJ et al. studied 105 renal transplant recipients.

Noncompliance was determined by cyclosporine level of less than 30 ng/mL, weight gain of more than 20% or missed clinic visits of more than 20%. The incidence of noncompliance in their study was about 54% [3]. Hilbrands LB et al. prospectively studied degree of noncompliance with immunosuppressive medications in 127 renal transplant recipients during the first year after transplantation by monthly pill counts. Noncompliance was defined by less than 80% adherence to the medication regimen. They reported a 23% frequency of noncompliance for cyclosporine in their patients [5]. Greenstein SM, and Siegal BR sent mail questionnaires to 2500 renal transplant recipients at 56 US transplant centers. Noncompliance was determined if patient reported one or more doses of immunosuppressive medications has been missed within the previous 4 weeks. The incidence of noncompliance reported by the 1402 respondents was 22.4% [6]. Nevins T, et al used electronic devices that recorded an event each time an azathioprine bottle was opened. They reported 11% noncompliance with azathioprine in their investigation [7]. In the present study we defined mild or minor noncompliance if patients missed 3 or more nonconsecutive immunosuppressive drug doses per months and severe or major noncompliance if they missed 3 or more consecutive doses per month, also if they stopped taking their medications for days, weeks or months. In our study the incidence of minor (mild) noncompliance was 7.7% and major (severe) noncompliance was 16.8%.

The compliance with immunosuppressive medications in renal transplant recipients have been measured by different methods, such as record review, sending mail questionnaires, interviews with direct questioning, prescription refill rates, pill counts, monitoring of drug concentration in sera and mechanical or electronic event monitoring. Except for electronic event monitoring which is the most accurate assessment way, other measurement methods are poor indicators of compliance with immunosuppressive medications. Electronic event monitoring is also mostly a research tool and is not a practical way in daily clinical practice.

One of the reasons of significant variation in the incidence of noncompliance is incomparable method of measurements that have been used in different studies. Most of the investigations were carried out with records review, sending mail questionnaires, serum CsA levels and interview with patients. In the present study we interviewed patients when they came for their clinic visit. Interview was performed in a private and confidently manner. The questionnaire was completed by transplant physician or transplant coordinator. The clinic records of patients were also reviewed for completion of necessary information. Due to limitations in methods of measurements the incidence of noncompliance in almost all studies have been underestimated. Greenstien and Siegal in their most comprehensive, largest and multi center study sent mail questionnaires to 2500 renal transplant recipients in 56 transplant centers of U.S. But only 1402 (56%) of transplant recipients responded. The incidence of noncom-

pliance reported by these respondents were 22.4%. The remaining 1098 (44%) were non respondents. As the incidence of noncompliance is expected to be higher in non respondents; so the real incidence of noncompliance in all patients together expected to be more than 22.4% [6].

The characteristics of study population has also a significant impact on the reported incidence of non compliance. The frequency of noncompliance has been higher in all studied pediatric renal transplant populations [8-9]. The high incidence of noncompliance has also been reported from transplant centers with higher rate of patients from lower socioeconomic class [10]. The study population should consist all consecutive transplant recipients of a center in order to include patients with functioning graft as well as those who has lost their grafts. In our study only patients coming to our renal transplant clinic were evaluated. In other words many noncompliant patients who lost their grafts or died were not included. This means that the real frequency of noncompliance in our transplant population is higher than 24.5% too.

The large numbers of studies have identified many predisposing or risk factors that are significantly more common in noncompliant renal transplant recipients such as younger age, lower socioeconomic class, lower level of education, addiction, depression and increased number of immunosuppressive drugs side effects.

Although none of these single risk factors have been found to predict noncompliance but when a several of these risk factors were present in a transplant recipient, the post transplant noncompliance with a high degree of probability will be predicted.

Analysis of data from our study have also identified some risk factors that have been significantly associated with immunosuppressive medications noncompliance. These include younger age, time since the date of transplant, lower level of education, low socioeconomic class and addiction or psychiatric disorders. Variables that did not show a significant correlation with medication noncompliance in our transplant recipients were: gender, marital status, sources of kidney donation, number of transplants and the immunosuppressive regimens.

In almost all of the studies it has been documented that young patients are more likely to be noncompliant [8-9-11]. In the study by Schweizer RT et al the incidence of noncompliance with immunosuppressive medications in patients younger than 20 was 57% compared with 15% in transplant recipients older than 40 years [12].

In our study patients noncompliant with immunosuppressive medications were significantly younger than compliant renal transplant recipients (35.5 ± 10.8 vs 39.8 ± 11.5 years, $P < 0.001$). The incidence of noncompliance in our patients with age 35 and younger was 31.4 % compared with 19.6% in transplant recipients older than 35 years ($P<0.05$).

The young transplant recipients often underestimate the benefits of immunosuppressive medications on their allograft outcome. The side effects of immunosuppressive medications are also less tolerated in young age, especially those that result in growth and cosmetic problems such as acne, warts, alopecia, hypertrichosis, gum hyperplasia, moon face, striae, obesity and cataract. These side effects may directly cause noncompliance or may result to depression then

to noncompliance [13].

We found longer time since the date of transplant to be a risk factor for noncompliance with immunosuppressive medications. In both of our noncompliant-minor and noncompliant-major groups the time since the date of transplantation were significantly longer than the time since the date of transplantation in compliant group. (73.2 ± 52.2 vs 83.2 ± 51.4 months, P <0.001 and 96.6 ± 65.4 months, P<0.001). Our findings are consistent with the result of study by Siegal B. and Greenstien S. who also found length of time since transplantation increases the possibility of noncompliance [14]. It seems patients underestimate the role of immunosuppressive medications when several years passes and the function of their graft remains well and stable.

It has also been documented that transplant recipients with lower level of education are more likely to be noncompliant with their immunosuppressive medications [11] and more education will increase their compliance [12]. We divided our 286 renal transplant recipients to 2 groups: 139 had lower level of education (45 illiterate, 94 elementary school) and 147 defined to have higher level of education (104 high school, 45 university training). The incidence of noncompliance-major was 64.6% in lower level education group compared with 35.4% in higher level education group (P<0.01).

In contrast to what is anticipated, noncompliance with immunosuppressive medications also is seen in highly educated renal transplant recipients. It is not true that well-informed transplant recipients are highly compliant. For example in liver and heart transplant recipients however the patients know that noncompliance with immunosuppressive medications means graft loss and death, still a higher rate of noncompliance is seen. Dew MA, et al studied 8 areas of compliance in 101 heart transplant recipients in the first year post transplant. The rate of persistent noncompliance during the year were 37% (exercise), 34% (monitoring blood pressure), 20% (medications), 19% (smoking), 18% (diet), 15% (having blood work completed), 9% (clinic attendance) and 6% (heavy smoking). Compliance in most areas deteriorated significantly over time (P<0.05). So increasing patient information is not enough to correct noncompliance [15].

Several investigators have shown poverty and lower socioeconomic status to be a strong predictor of noncompliance in renal transplant recipients [12-16-17]. In our study 118 renal transplant recipients were from lower socioeconomic class, 95 from middle class and only 73 were from higher socioeconomic class. The incidence of noncompliant-major was 23.7% in lower socioeconomic class compared with 2.7% in higher socioeconomic class (P<0.05).

The expenses of renal transplantation and immunosuppressive drugs exceed what many people from developed countries and the majority of people from developing countries can afford. According to Gaston RS, in U.S. the government and the insurance programs provide necessary financial assistance for renal transplantation and immunosuppressive medications. The average cost of immunosuppressive regimen in U.S. for a renal transplant recipient taking cyclosporine Neoral 4 mg/kg/d and mycophenolate mofetil 2g/day is $ 13.550 per year. About 10% of renal transplant recipients have no access to different insurance programs. Some of these patients who

can not obtain immunosuppressives due to financial hardship will be predisposed to noncompliance and graft loss [18]. Sanders CE, et al reported a significant risk of late acute rejection and graft loss in a subgroup of disadvantaged renal transplant recipients whose cyclosporine was tapered or discontinued because of financial reasons [16].

In Iran as a developing country, government pays for all hospital expenses of renal transplantation [19]. The major immunosuppressive medications such as cyclosporine Neoral and mycophenolate mofetil are made available for each renal transplant recipient in a very reduced price. The average expenses of CsA Neoral and mycophenolate mofetil for every transplant recipient per month is $ 2 and $ 25 respectively. Nearly all of transplant recipients can afford it. If a patient had financial problem in obtaining his major immunosuppressive medications there are charity foundations to make his drugs available for him free of charge. So the higher incidence of noncompliance in our low socioeconomic class renal transplant recipients is not due to high expense of immunosuppressive medications.

Several investigators have documented that psychiatric disorders, history of substance abuse, poor social support, depression and stress to increase the risk of noncompliance to medications in transplant recipients [20-21-22]. Fourteen of our patients were heavy smokers and opiate addicts and 15 of them had some type of psychiatric disorders. The incidence of these disorders were 22.9% in our noncompliant-major group as compared to 7.4% in compliant group ($P<0.05$).
Sex, marital status, sources of kidney donation, number of transplantations and type of immunosuppressive protocols which has been reported to be predisposing factors by some investigators did not show significant correlation with incidence of immunosuppressive drug noncompliance in our study.

Most of the investigators have also reported the same level of noncompliance in their male and female renal transplant recipients [6-12]. But some others have reported male or female patients to be less compliant [3-23]. We found similar rates of noncompliance in male and female patients (23.5% vs 25.9%).

In some studies the rate of compliance and noncompliance have differed significantly on the basis of marital status [22-23]. The rate of noncompliance in our married and unmarred renal transplant recipients were 24.2% vs 25.4%.

Regarding sources of kidney donation, in almost all studies no significant difference in the incidence of noncompliance in transplant recipients of cadaveric versus living related donor kidney have been found [12]. In Iran, as has been previously published, we have adopted a controlled living unrelated donor renal transplantation program in 1988. By transplanting all renal transplant candidates we have eliminated renal transplant waiting list by the end of 1999. The sources of kidney donations in Iran is 76.7% from living unrelated donor, 22.5% from living related donor and only 0.8% from cadaveric kidneys [19-24]. We compared the incidence of noncompliance between 209 renal transplant recipients from living unrelated donor and 76 from living related donor and there was no significant difference (24.9% vs 23.7%).

Frazier et al. have shown more noncompliance in patients with retransplant [22]. But as in many

other studies we found no correlation between retransplant and immunosuppressive medication noncompliance. The incidence of noncompliance in our patients with first transplant was 8.3% compared with 8.6% in those with second transplant.

The higher incidence of noncompliance with different immunosuppressive protocols have been related to side effects or drug expenses. Hilbrands LB et al. showed better compliance for prednison in men as compared with women [5]. Also young patients do not tolerate cosmetic side effects of immunosuppressive drugs [13]. Sanders CE, et al showed the cost of CsA was a risk factors for noncompliance and graft loss [16]. We found no increased incidence of noncompliance between 177 patients, who were on CsA, azathioprine and prednisone compared with 97 patients who were on CsA, mycophenolate and prednisone.(22% vs 25.8%).

Noncompliance with immunosuppressive medications results in higher rate of acute rejection episode, graft dysfunction, graft loss and patient death. Schweizer RT et al showed that 91% of kidney transplant recipients who were noncompliant with medications and follow up care either lost their grafts or died [12]. De Geest S, et al reported more late acute rejection episodes in noncompliant group. They also showed that 5 years graft survival in non compliant group was significantly lower than the compliant group [23]. Didlake RH, et al documented, noncompliance with immunosuppressive medication, in renal transplant recipients to be the third leading cause of graft loss after rejection and systemic infection [1].

In our study the rate of acute rejection episodes in noncompliant group increased 4.8 fold compared with compliant renal transplant recipients ($P<0.001$). The incidence of severe allograft dysfunction (defined by serum creatinine level of > 5.0 mg/dl) was also significantly increased in noncompliant group compared with compliant renal transplant recipients (14.3% versus 7.9% $P<0.01$). As our study was carried out only on transplant recipients coming to renal Transplant clinic. Data on patients who lost their graft or died due to immunosuppressive medications noncompliance were not included.

As immunosuppressive medications noncompliance is a significant risk factor for acute rejection, graft loss and patient death the following strategies should be adopted in order to prevent noncompliance in transplant recipients:

1- Better patient selection. Those with drug addiction should not be accepted for transplantation.
2- More patient teaching regimen. Some investigators believe the compliance will improve if the patient better understand the relation of immunosuppressive medication to his transplant outcome.
3- The treatment of depression and stress will improve compliance.
4- If noncompliance is the result of side effect of one of immunosuppressive drugs. That medication is better to be withdrawn or be replaced by similar drug without that side effect (CsA to be replaced by Tacrolimus in gingival hyperplasia).
5- Simplified medication regimen: the number of unessential drugs should be reduced and the frequency of drug administration per day also should be decreased.
6- The number of clinic visits to be increased. It

has been shown that compliance improves after each clinic visit.

7- All transplant recipients should have access to immunosuppressive medications without financial problems

8- Regular assessment of medication noncompliance.

Before performing this study we were not aware that so many of our patients were noncompliant with their immunosuppressive regimen. We were surprised when so many of our transplant recipients disclosed their medication noncompliance.

References:

1. Didlake RH, Dreyfus K, Kerman RH, Van Buren CT, Kahan BD. Patient noncompliance: a major cause of late graft failure in cyclosporine treated renal transplants. Transplant Proc 1988; 20: (suppl 3) 63-9
2. Uehling DT, Husseay JL, Weinstein AB, Wank R, Bach FH. Cessation of immunosuppression after renal transplantation. Surgery 1976; 79: 278-82
3. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. Transplantaion 1993; 55: 51-6
4. Ghods AJ, Ossareh S, Khosravani P. Comparison of some socioeconomic characteristics of donors and recipients in a controlled living unrelated donor renal transplantaion program. Transplant Proc 2001; 33: 2626-7
5. Hilbrands LB, Hoitsma AJ, Koene RAP. Medication compliance after renal transplantation. Transplantation 1995; 60: 914-20
6. Greenstein S, Siegal B. Compliance and noncompliance in patients with a functioning renal transplant: A multicenter study. Transplantation 1998; 66: 1718-26
7. Nevins T, Thomas W, Skeans M. et al Medication compliance following renal transplantaion: the natural history. Transplantation 1999; 67: S115
8. Blowey DL, Hebert D, Arbus GS, Pool R, Korus M, Koren G. Compliance with cyclosporine in adolescent transplant recipients. Pediatr Nephrol 1997; 11: 547-51
9. Meyers KE, Thomson PD, Wiland H. Noncompliance in children and adolescents after renal transplantation. Transplantion 1996; 62: 186-9
10. Butkus DE, Meydrech EF, Raju SS. Racial differences in the survival of cadaveric renal allografts: overriding effects of HLA matching and socioeconomic factors. N Engl J Med 1992; 327: 840-5
11. Sketris I, Waite N, Grobler K, West M, Gerus S. Factors affecting compliance with cyclosporine in adult renal transplant patients. Transplant Proc 1994; 26: 2538-41
12. Schweizer RT, Rovelli M, Palmeri D, Vossler E, Hull D, Bartus S. Noncompliance in organ transplant recipient. Transplantation 1990; 49: 374-7
13. Cochat P, De Geest S, Ritz E. Drug holiday: a challenging child – adult interface in kidney transplantation. Nephrol Dial Transplantation 2000; 15: 1924-7
14. Siegal BR, Greenstein SM. Postrenal transplant compliance from the perspective of African–Americans, Hispanic–Americans, and Anglo-Americans. Adv Ren Replace Ther 1997; 4: 46-54
15. Dew MA, Roth LH, Thomyson ME, Kormos RL, Griffith BP. Medical compliance and its predictors in the first year after heart transplantation.J Heart Lung Transplant 1996;15:631-45
16. Sanders CE, Curtis JJ, Julian BA, et al. Tapering or discontinuing cyclosporine for financial reasons – a single center experience. Am J kidney Dis 1993; 21: 9 - 15
17. Kalil RSN, Heim-Duthoy KI, Kasiske BL. Patients with a low income have reduced renal allograft survival. Am J Kidney Dis 1992; 20: 63-9
18. Gaston RS. Noncompliance in solid organ transplantation. Curr Opin Organ Transplant 2001; 6: 164-8
19. Ghods AJ, Renal transplantation in Iran. Nephrol Dial Transplant 2002; 17: 222-8
20. Bunzel B, Laederach-Hofman K. Solid organ transplantation: are there predictors for posttransplant noncompliance ? a literature overview. Transplantation 2000; 70: 711-6
21. Shapiro PA, Williams DL, Foray AT, Gelman IS, Wukich N, Sciacca R. Psychological evaluation and prediction of compliance problems and morbidity after heart transplantation. Transplantation 1995; 60: 1462-6
22. Frazier PA, Davis-Ali SH, Dahl KE. Correlates of noncompliance among renal transplant recipients. Clin Transplant 1994; 8: 550-7
23. De Geest 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
24. Ghods AJ, Ossareh S, Savaj S. Result of renal transplantation of the Hashemi Nejad Kidney Hospital –Tehran. In : Cecka JM, Terasaki PI ed. Clinical Transplant 2000. Los Angeles : UCLA Tissue Typing Laboratory,2001:203-10