SIDE EFFECTS OF CYCLOSPORINE COMPARED TO TACROLIMUS AMONG YEMENI KIDNEY TRANSPLANT PATIENTS WHO SHARE THE SAME ADJUVANT AGENTS: MYCOPHENOLATE MOFETIL AND PREDNISONE

ABSTRACT

Background: A renal allograft is the best therapeutic alternative for patients with end stage renal diseases. Nonetheless, rejection still represents a great challenge. In order to overcome this issue, therapeutic strategies include the combined use of immunosuppressive and anti-inflammatory agents, but they are not exempt from complications . Interestingly, the major cause of morbidity and mortality after the first transplanted year are due to disorders unrelated directly to immunologic etiology or disease related to immunosuppressive drugs. **Objectives:** The purpose of this study is to determine the side effects in renal transplant Yemeni patients adherence to cyclosporine compared to tacrolimus sharing the same adjuvant agents which are mycophenolate mofetil "MMF" and prednisone. **Subject and methods**: This study was carried on 100 kidney transplanted Yemeni patients divided into two groups: cyclosporine group (n=50) and tacrolimus group (n=50), each member of these groups was visited three times, blood samples was collected for biochemical functions including fasting blood sugar, liver enzymes, kidney functions, lipid profiles and white blood cells counts. Body weight and blood pressure had been examined; clinical complications were also estimated by a medical records. **Results:** This study showed that serum total and direct bilirubine, gamma glutamyl transferase "GGT" and lipid profiles were elevated in cyclosporine group, whereas in tacrolimus group they were within normal range. The incidence of complicated events reported as follows: Hairtusim, gum hyperplasia, herpeszoster, coushing face and obesity were obviously present in cyclosporine group, while in tacrolimus group diabetes mellitus, hair loss and gastrointestinal tract infections were exist. **Conclusion**: This study found that a tacrolimus-based treatment was significantly better than an immunosuppressive regimen based on cyclosporine due to the generally less side effects associated with tacrolimus, despite its effect on increasing diabetes among kidney transplant patients.

Keywords: Renal transplant, cyclosporine, tacrolimus, mycophenolate mofetil "MMF", prednisone, side effects, Yemen

INTRODUCTION

Kidney transplantation is the preferred treatment for most patients with end-stage kidney disease (ESRD)[1]. Kidney transplantation for patients with ESRD can improve endurance and quality of life, and lower the cost of health care. Currently, the 1-year patient survival rates and graft survival rates are 94% and 82%, respectively[2,3]. The incidence of ESRD in Yemen is 120 cases per million annually, which is comparable to the incidents reported in other posts in the same region[4,5,6]. In Yemen, the kidney transplant program began intermittently since 1998. However, there has been a well-established program that has been running regularly since the beginning of 2005 in the Urology and Nephrology Center at Al-Thawra Modern General Hospital, Sana'a[7]. Despite significant advances in the field of kidney transplantation, long-term graft survival has not increased significantly due to the continuing effect of immunosuppressive and infectious disease on transplant recipients [8,9]. Several immunosuppressive agents are currently in use in protective immunity in kidney transplant recipients. Commonly used oral immunosuppressive agents fall into three categories: calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative agents (azathioprine and mycophenolate mofetil) and steroids (prednisone). The combined use of one agent in each class is known as triple therapy, and it is the standard regimen for early to mid-term immunosuppression after transplantation. This provides broad immunosuppression based on the different mechanisms of action for each group [10]. Medicines are not without challenges and risks. Recipients need to continue to take immunosuppressive drugs for the rest of their lives to prevent allograft rejection, and this trade in morbidity and mortality from organ failure to risks of infection and cancer. In addition, these drugs are likely to contribute to increased mortality from cardiovascular disease, which is the leading cause of premature death in kidney transplant recipients [10]. Cyclosporine A (CyA) and tacrolimus (TAC), as calcineurin inhibitors, are used at the time of transplantation to achieve adequate immunosuppression and to prevent acute episodes of rejection [3]. CyA was revealed

in 1971, and in 1983, this drug was permitted for the prevention of organ transplant rejection. TAC (Prograf) was discovered in the early 1980's and from 1989, and is used to prevent liver transplant rejection. After that, the use of this drug quickly developed for transplantation of other organs[11]. Because of the possibility of different effects in Yemeni patients compared to other nationalities, and also that there was no study on this topic in advance in Yemen, so this follow-up study was done with the aim of evaluating the differences in kidney transplant patients, who share the same immunosuppressive adjuvants, which are mycophenolate mofetil. MMF '+ prednisone but differs in the calcineurin inhibitor, one group used cyclosporine and another group used tacrolimus regarding its effect on kidney and liver function, lipid properties, and complete blood cell count. Also investigating the possible relationship between the groups cyclosporine and tacrolimus with respect to other clinical side effects such as hypertension, diabetes, obesity, and dysmorphic changes.

SUBJECTS AND METHODS

This study was conducted at Al-Thawra Hospital and the National Center for Public Health Laboratories in Sana'a on one hundred Yemeni patients with kidney transplants ranging in age (14 - 60 years): 59 men and 41 females between September 2016 to September 2017. They were divided into two groups: (Group A) 50 patients (39 males, 11 females) on a cyclosporine-based immunosuppressant regimen, (group II) 50 patients (20 males and 30 females) with a tacrolimus-based immunosuppressive regimen. All patients were informed of the aim of the study and gave their consent.

Both drugs were administered in two divided doses and the dose was adjusted according to clinical responses and blood trough levels for 12 hours. The whole blood trough level of tacrolimus was maintained between 5-15 ng / ml and cyclosporine between 100-200 ng / ml. Doses were tapered based on the concentration of the drug in whole blood and clinical examination.

Sample processing: Blood samples were drawn for all measurements in the morning from 8 am to 11 am. Two tubes with EDTA one for cyclosporine or tacrolimus and the second for CBC, another plain tube for chemical parameters. Analysis was performed on the same day of collection and results were recorded at three-month intervals. The samples were taken for analysis of cyclosporine and tacrolimus blood levels, fasting blood sugar, kidney function tests (KFT)including urea and creatinine tests, liver functions tests (LFT) included bilurubine total and direct,glotamate oxaloacetate transaminase GOT, glutamate pyruvate transaminase GPT,alkaline phosphataes ALK, and gamma glutamate transaminase GGT tests , lipid profiles (total cholesterol, high density lipoprotein ,low density lipoprotein and triglyceride) also the complete blood count CBC were determined. Blood pressure and body weight were also recorded with an automatic scale. Data from the renal recipient records were investigated retrospectively to determine the immunosuppressant complications among the renal allograft recipients.

Ethical consideration: Ethical approval was obtained from the Ethical Committee of the medical research at Sana'a University. Approval was obtained from all participants before recruiting them to the study and after explaining for them the aim of the study.

Statistical analysis: Data of completed questionnaire obtained, and were manipulated using Statistical Package for the Social Science version 21.0 software (SPSS version 21.0).

RESULTS

The recipient's age, ranged from 14-60 years and their mean age was 32.4 years in both groups. A significant difference was only found in recipients aged at > 45 years as in cyclosporine group was 16% while in tacrolimusit it was 8%. Regarding to gender 78% male and 22% female have been found in cyclosporine group while in tacrolimus group were 40% male and 60% female [Table 1]. Their causes of renal failure was clinically diagnosed as follows: Hypertension (37%), Kidney atrophy (14%), Chronic urinary tract infection (14%), Stones (10%), Antibiotic abuse (4%), Hereditary (4%), Diabetes mellitus (3%), and (14%) unknown cause [Table 2]. All renal recipients were received a single kidney from a living donors aged between 18-55 years, in cyclosporine group (46%) of the donors were relatives and (54%) were unrelatives , while in tacrolimus group (72%) of the donors were relatives and (41%) were unrelatives. Also the drugs levels were similar in both groups; 62% and 64% of the cyclosporine and tacrolimus respectively were within normal ranges of the trough blood level which is 100-200 ng/ml for cyclosporine and 5-15 ng/ml for tacrolimus, and 38% in cyclosporine group and 36%in tacrolimus group were have

been shifted from their trough blood level [Table 3]. The post transplant means values of sugar, LFT, KFT, and lipid profiles are summarized in [Table 4], the significant difference were found in the elevation of total and direct bilirubin, GGT, total cholesterol, LDL, HDL, and triglycerides in cyclosporine group while not in tacrolimus group (P<0.0001). No differences in the other test biochemical's parameters were detected between the two groups as shown in table 4. There was a significant difference in Hb (p<0.0001) and Plts (p<0.023) while no difference had been found in WBCs between the two groups [Table 5]. The incidence of adverse events reported in Table 6 included: 64% hairtusim, 54% obesity, 16% gum hyperplasia , 22% couching face, 10% herpes zoster, 28% herpes simplex, and 2% Kaposi sarcoma were associated with cyclosporine group, and this was significant. On the other hand gastrointestinal infection 24%, DM 20%, hair loss 20% ,10% gastritis and had been found in tacrolimus group while not in cyclosporine group.12% of cyclosporine group and 8% of tacrolimus group had no complications during the follow up time (one year).

DISCUSSION

The results of this study showed that the fasting blood sugar levels in both groups were similar and at the top of their normal range. Although, diabetes mellitus as a clinical complication is appeared in 20% of tacrolimus group whereas in cyclosporine group was only 2%. This is in agreement with the fact that after renal transplantation some 45% of patients may show abnormal glucose tolerance and 20–25% may develop diabetes[12]. Another study showed that tacrolimus is associated with diabetes mellitus, due to the increased concentration of FKBP (FK binding protein) in pancreatic islets relative to cyclophiline during drugs metabolism. Morphologic changes in the islets include cytoplasmic swelling, vacuolization, and apoptosis, with normal immune-staining for insulin, this effect is dose related and may be exaggerated by concomitant corticosteroid use especially prednisone [13]. Some previous studies suggested that tacrolimus influences glucose metabolism by reducing pancreatic insulin secretion in a dose-dependent manner [14] . Initially, an increased insulin resistance was also reported[15], but this seems to be the result of the co-administration of steroids [14]. Both prednisone and calcineurin – inhibitors provide additional risk factors, with tacrolimus conveying an increased risk, as compared to cyclosporine. Corticosteroids have been shown to produce peripheral insulin resistance and to cause alteration in pancreatic beta-cell insulin secretion. Cyclosporine and tacrolimus also appear to alter peripheral insulin sensitivity and to diminish islet function[16].

In the current study, the mean serum values of urea and creatinine were at the upper limit of their normal range. This is supported by another study, which reported that both cyclosporine and tacrolimus produce a chronic arteriolopathy and chronic toxicity with irreversible kidney damage [17] and this elevation indicate a significant, potentially graft-endangering event[18]. The calcineurin inhibitors CsA and FK506 produce a dose –related reversible renal vasoconstriction that particularly affects the afferent arteriole, the glomerular capillary ultrafiteration coefficient also decreases .Most of the studies on the mechanism of this effect have used cyclosporine rather than tacrolimus[19].This have explained why cyclosporine affect on kidney function is obvious, as the main adverse effect caused by cyclosporine is nephrotoxicity, the long term use of CsA can result in a chronic toxicity associated with irreversible and progressive decrease in renal function and this characterized by tubular –interstitial fibrosis and hyaline degenerative changes in the afferent arteriole walls [20], this lead to vasoconstriction that causes acute reversible decrease in GFR" glumerular filtration rate " [21].

Although this study have shown that the blood concentration of urea and creatinine were higher in tacrolimus group (urea: 7.99± 8.3, creatinine: 116 ± 74.7) than in cyclosporine group (urea: 6.18 ±2.1, creatinine: 113± 32.5) , this is not agreement with some studies that indicated tacrolimus and MMF" mycophenolate mofetil " significantly improved kidney function [22] , and the serum creatinine concentrations were better in tacrolimus group ,due to MMF [23] .But agreement with a study reported that ,the majority of renal transplant patients tolerate long-term cyclosporine therapy without evidence of progressive toxic nephropathy [24].

There was a significant increase in total, direct bilirubin blood levels and gamma glutamyl transpeptidase "GGT" in cyclosporine group rather than tacrolimus group .This is in agreement with the study reported that episode of hepatic dysfunction typically manifesting as sub clinical, mild, self limiting, and dose-dependant elevations of serum aminotransferase levels with mild hyperbilirubinemia may occur in nearly half of all kidney transplant recipients taking cyclosporine and occur

less frequently in those taking tacrolimus. No specific hepatic histologic lesion has been described in humans, and the hyperbilirubinemia is a reflection of disturbed bile secretion rather than hepatocellular damage, cyclosporine doesn't itself produce progressive liver disease; other cause, most frequently one of the viral hepatitis[25]. Even some studies found that both cyclosporine and tacrolimus cause hepatotoxicity and liver dysfunction [26, 27] .

Lipid profiles including total cholesterol, HDL, LDL, TG were significantly altered with cyclosporine and elevated in comparison to tacrolimus group in the current study .This results were similar to those obtained by another studies which assessed hyperlipidemia is one of the metabolic a adverse effects of cyclosporine and tacrolimus but its greater in cyclosporine A than in tacrolimus the mechanism related to cyclosporine alteration of lipids is through its direct effect on cell membrane cholesterol concentration and regulatory pools ,resulting in both increased synthesis of cholesterol and decreased clearance of LDL, HDL levels are typically normal or elevated in the obesity ; however cardio protective HDL fraction may remain low [28, 29, 30].

The total blood cell counts were similar in the two study groups, and this is in agreement with another studies that assessed cyclosporine A and corticosteroids have no suppressor effects on bone marrow cells, also mycophenolate mofetil usually do not cause bone marrow suppression[31], even if another study found that prednisone inhibited the expression of polymorphoneutriphils to the tissue .This lead in turn to their accumulation in the peripheral blood [32]. Even sever anemia is appeared due to selective depression of erythropoiesis by immunosuppressive drugs[33], anemia resolved when tacrolimus was replaced with cyclosporine , more generalized bone marrow suppression has also been reported [34], this result was shown a significant difference between the two groups , although hemoglobin was within normal range ,as the excellent graft function is achieved ,a burst of erythropoietin secretion is normally followed by effective production of erythrocytes[35] . There was a significant difference in platelets between the two groups, it seems to be thrombocytosis in cyclosporine group, but this is not a greeted with a report said that thrombocytopenia is associated with cyclosporine therapy[36].

There was a significant presence of gingival hyperplasia or gum hyperplasia in cyclosporine group while not in tacrolimus group. These findings are consistent with the results obtained from other studies which reported that cyclosporine is well known to be associated with the development of gingival overgrowth[37] ,the reason for the localization of this effect to the gingival is unknown , its possible that the gingival tissue is exposed to higher concentrations of drug than other tissues , and this is substantial evidence that the drug acts on the growth and function of both gingival fibroblast and gingival epithelial cells via cytokines and growth factors [38]. CsA may also cause gingival hyperplasiaby increasing the number of fibroblasts and the production of collagen by them [39].

It was shown that hairtusim is significantly incidence in cyclosporine group while hair loss significantly found in tacrolimus group, and these were supported by another study that reported hairtusim found in cyclosporine [40] and hair loss in tacrolimus[41]. CsA may cause hypertrichosis on the face, arms, shoulders, and back, and is particularly troublesome in young women and children, particularly if dark-haired. This disorder is dose-dependent, and, at least in experimental animals, seems to be related to the inhibition of NFAT in follicular keratinocytes [42].

A significant difference in herpes zoster and Kaposi sarcoma and dysmorphic changes that were found more in cyclosporine in the current study. This is in concordance with the results obtained by another worker who found that the herpes zoster develops in approximately 10% of adult renal transplant recipients and may involve two to three adjoining dermatomes; infection is usually caused by reactivation of latent diseases. Post transplanted infection can be primary or transmitted from the donor kidney and is associated with Kaposi sarcoma occurring a median of 30 months post transplant, diagnosis is supported by pathology and by the presence of human herpes viruses[43] .

There was no significant difference in hypertension as a complicated disease' between cyclosporine and tacrolimus groups and this is supported by other studies reported that hypertension is a common after transplantation and may be caused by the effect of cyclosporine or tacrolimus [44], Cyclosporine may cause renal vasoconstriction through several mechanisms [45]. As a

consequence, there is a reduction of glomerular filtration rate and of renal blood flow [46] . In turn, these functional abnormalities lead to retention of salt and water, to an increase in extracellular fluids, and to an increased cardiac output[47]. The apparently normal production of renin by the allograft and by the native kidney is inappropriately elevated in a setting characterized by extracellular fluid expansion, collaborating with hypertension [48]. Tacrolimus also produces clinical post-transplant hypertension via mechanisms similar to those of cyclosporine [49] although hypertension is less common in patients given tacrolimus than in those receiving cyclosporine [50]. There is a significant difference in obesity in the two study groups, it was clearly obvious in cyclosporine group due to high appetite in these patients and this is associated with steroid therapy that potentate in combination with cyclosporine [51].

CONCLUSION

This study found that a tacrolimus-based treatment was significantly better than an immunosuppressive regimen based on cyclosporine due to the generally less side effects associated with tacrolimus, despite its effect on increasing diabetes among kidney transplant patients. We also hope to conduct more studies to prevent widespread renal failure by knowing the factors predisposing to kidney failure and researching factors that can affect medical compliance after kidney transplantation in Yemen.

AUTHOR'S CONTRIBUTION

This research work is part of the MA thesis. The candidate, Ibtisam Al-Akwa, conducted the laboratory work and wrote the thesis. The second author (NAS) conducted and supervised the clinical works. The Corresponding Author (HAA), Third Author (KAM), and the rest of the authors oversaw the work, reviewing and editing the draft and manuscript.

ACKNOWLEDGMENTS

Authors acknowledge the financial support of Sana'a University, Sana'a City, Yemen.

CONFLICT OF INTEREST

"No conflict of interest associated with this work".

REFERENCES

1-Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: Meta-analysis and meta-regression of randomised trial data. BMJ 2005;331:810

2-Tsipotis E, Gupta NR, Raman G, Zintzaras E, Jaber BL. Bioavailability, efficacy and safety of generic immunosuppressive drugs for kidney transplantation: A systematic review and meta-analysis. Am J Nephrol 2016;44:206-18

3-Liu JY, You RX, Guo M, et al. Tacrolimus versus cyclosporine as primary immunosup-pressant after renal transplantation: A meta-analysis and economics evaluation. Am J Ther 2016;23:e810-24

4- Nassar Mogahid Yahi'a, Al-Shamahy Hassan Abdulwahab, Al-Samawi Abdullah Saleh; Abu Asba, Nagieb Waza'a, El-Nono Ibrahiem Husain, Masood Haitham Abdulwahab. Human Leukocyte Antigen Class I and II Variants in Yemeni Patients with Chronic Renal Failure. Iran.J.Immunol. 2017; 14(3):1-6.

5- Nassar MY, Al-Shamahy HA, Haitham A. A. Masood. The Association between Human Leukocyte Antigens and Hypertensive End-Stage Renal Failure among Yemeni patients. Sultan Qaboos University Med J, 2015;15 (2):e241–249.

6- Sahman M, Al-Mousawi M, Hayati H et al. Result in 158 consecutive cadaveric renal transplantation. Transplant proc 2005; 37:2965-2966.

7- El-Nono IH, Al-Ba'adani TH, Abu Asba NW et al. Adult -to-adult living related donor, renal transplantation in Yemen : The first experience .Saudi J kidney Dis Transplant 2007;18(2) : 265-269.

8- Liu H, Chou M, Kao M. Allograft dysfunction in association with cytomegalovirus in renal transplant recipient. Division of Nephrology, Department of Internal Medicine, China Medical College Hospital, Taichung, Taiwan, R.O.C. 2003; 17 (2): 95-98.

9- Weikert CB, Blumberg AE. Viral Infection after Renal Transplantation: Surveillance and Management. Clinical Journal of the American Society of Nephrology. 2008; 3: S76–S86.

10- Vicenza CR, Vicenza SC, Bergamo GR. Kidney Transplantation: Strategies to Prevent Organ Rejection; 2005; VII.

11- Penninga L, Møller CH, Gustafsson F, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: Systematic review with meta-analyses and trial sequential analyses of randomised trials. Eur J Clin Pharmacol 2010;66:1177-87.

12-Mathew TH, Rao M, Job V et al. Post-transplant hyperglycemia: a study of risk factors. Nephrol Dial Transplant 2003; 18: 164–71.

13-Drachenberg CB, Klassen DK, Weir MR, Wiland A, Fink JC *et al.* Islet Cell Damage Associated With Tacrolimus And Cyclosporine: In Morphological Features In Pancreas Allograft Biopsies And Clincal Correlation. Transplantation: 1999; 68: 396-402.

14-Boots JMM, Van Duijnhoven EM, Christiaans MHL *et al.* Glucose metabolism in renal transplant recipients on tacrolimus: the effect of steroid withdrawal and tacrolimus trough level reduction. J Am Soc Nephrol 2002, 13:221.

15-Mayer A. Chronic rejection and graft half-life: five-year follow- up of the European tacrolimus multicenter renal study.Transplant Proc 2002; 34:1491.

16-Fort E, Mercadal G, Berlana D, Martorell C, Badia MB, Gil-Vernet S, Jòdar R. Diabetes mellitus associated with tacrolimus in renal transplant.The European Journal of Hospital Pharmacy Science 2005; 11: 74 –77.

17-Silva FR, Silva LB, Cury PM, Burdmann EA, Bueno V. FTY720 in combination with cyclosporine is analysis of skin allograft survival and renal function .International immunopharmacology 2006; 6:1911-1918.

18-Amend WJ, Vincenti F, Tomalnovich SJ. The first three posttranspalnt month's. Handbook of KT 2005; 8:213-228.

19-Danovitch GM. Hand book of kidney transplantation 4th edition. 2004; 72-134.

20-Campanholle G, Galvao M,Cenedeze MA, DepaulV, Teixeira A,dosreis MA. Dual response of animals with chronic cyclosporine nephrotoxicity to an acute hemic injury. Transplantation proceedings 2006; 38, 3341-3343.

21-Kopp JB, Kloman PE. Cellular and Molecular-Mechanisms of Cyclosporine Nephrotoxicity .J AM SOC Nephrol 1990; I: 162-179.

22-Stegall MD, Simon M, Wachs ME et al. Mycophenolate Mofetil decrease rejection in simultaneous pancreas-kidney transplantation when combined with tacrolimus or cyclosporine. Transplantation 1997; 64:1695.

23-Morris-Stiff G, Khan A, Quiroga I, Baboo R,Jurewicz WA. Immunosuppression in renal transplantation BMJ 1999; 319:1136.

24-Burke JF, Pirsch JD, Ramos EL, Salmon DR, Stablem DM, Van Duran DH, West JC. Long –term efficacy and safety of cyclosporine in renal transplant recipients .The New England journal of medicine 2007; 331:358-363.

25-Armin W, Ursula S, Alfred F, Lothar A, Andre C, Wolfang ET, Gert F. Hepatocellular Effects of Cyclosporine A and it's Derivative SDZ IMM 125 in Vitro .The Journal of Pharmacology and Expemintal Therapeutics 1998; 284:817-825.

26- Martendels 32 .The complete drug reference 1999; 519-525

27- Fabrizi F, Bunapradist S, Martin P. Kidney transplantation and liver disease. Handbook of kidney transplantation 2005; 11: 335-343.

28-Guichard SW. Nutrition in the kidney transplant recipient. Handbook of KT 2005; 18:477-478.

29-Muller T ,Koeppe S ,Al-beitrer K, Lucker D, Salzer U ,Blazar E, Aufricht C .Pediatric nephrology. 2003; 18: 939-942.

30-Akman UM, Afsar B, Sezer.S , Ozdemir FN, Haberal M. Lipid profile during Azathioprine or Mycophenolate Mofetil combinations with cyclosporine and steroids. Transplantation proceeding 2007; 39: 135-140.

31-Danovitch GM. Immunosuppressive medications and protocols for kidney transplantation .Hand book of kidney transplantation 4th edition 2005; 4: 72-91.

32-Benjamin E, Coico R, Sunshine G. Immunology .a short course. 4th edition.2000; 389-390.

33-Winkler M et al. Anemia associated with FK 506 imunosuppression. Lancet 1993:341:1035-1036.

34-De-La-Sera HC et al. Tacrolimus –induced bone marrow suppression. Lancet 1997; 350:741-15.

35-Sollinger HW. US renal transplantation Mycophenolate Mofetil study group for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995; 60:225-232.

36-Dejong DJ, Sayler DJ. Possible cyclosporine–associated thrombocytopenia .DICP Ann Pharmacother 1990; 24:1007.

37-Brunet L , Miranda-Rius, Farre M, *et al.* Gingival enlargement induced by drugs. Drug safety 1996; 15:219-31.

38-Stefanidou V,Liakopoulos V,Eleftheriadis T,Anifandis G,Mertens PR *et al.* Expression of transforming growth factor-receptor II m RNA in cyclosporine–induce gingival overgrowth .Transplantation Proceedings 2006; 38:2905-2908.

39-Chand DH, Quattrocchi J, Poe SA, *et al*. Trial of metronidazole vs. azithromycin for treatment of cyclosporine-induced gingival overgrowth. Pediatr. Transplant 2004; 8: 60–64.

40-Montagnino G, Kramer BK. Efficacy and safety of tacrolimus compared with cyclosporin microemulsion in kidney transplantation: twelve-month follow-up. Transplant Proc 2002; 34: 1635–1637.

41-Raimund M. Efficacy and safety of tacrolimus compared with cyclosporin microemulsion in renal transplantation: a randomized multicentre study. Lancet 2002; 359: 741–746.
42-Gafter-Gvili A, Sredni B, Gal R, *et al*. Cyclosporin A-induced hair growth in mice is associated with inhibition of calcineurin- dependent activation of NFAT in follicular keratinocytes. Am J Physiol Cell Physiol 2003; 284: C1593–603.
43-Kubak BM, Maree C. Pegues DA, Hwany A. Infection in kidney transplantation .Handbook in kidney transplantation 2005; 10:280-329.

44-Prisch JD,Sollinger HW, Smith C. Kidney and Pancreas transplantation in diabetic patients. Handbook in kidney transplantation 2005; 14:391- 398.
45-Bartholomeusz B, Hardy KJ, Nelso AS, Philips PA. Modulation of nitric oxide improves cyclosporine A-induced hypertension n rats and primates. J Hum Hypertens 1998; 12: 839–844.
46-Morales JM, Andres A, Rengel M, Rodicio JL. Influence of cyclosporin, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation. Nephrol Dial Transplant 2001; 16: 121–4.
47-Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation. ransplantation 2001; 72: 9–12.

48- Curtis JJ. Posttransplant hypertension. Transplant Proc 1998; 30: 2009–2011.
49-Margreiter R. European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. Lancet 2002; 359: 741–746.

50-Henry ML. Cyclosporine and tacrolimus (FK 506). A comparison of efficacy and safety profiles. Clin Transplant 1999; 13: 209–20.
51-Siddqi N, Hairharan S, Danovitch G .Evaluation and preparation of renal transplant candidates .Hand book of kidney transplantation 2005; 6:170-183.

Table 1: The patient characteristics :

Character	Cyclosporine group		Tacrolimus group		Total	
	No	%	No	%	No	%
Sex:						
Male	39	78	20	40	59	59
Female	11	22	30	60	41	41
Total	50	100	50	100	100	100
Age group:						
< 15 years	0	0	1	2	1	1
15-25 years	15	30	18	36	33	33
26-35 years	16	32	17	34	33	33
36-45 years	11	22	10	20	21	21
>45 years	8	16	4	8	12	12
Total	50	100	50	100	100	100

Table 2: The original causes of renal failure among our study group :

Character	**Cyclosporine group**		**Tacrolimus group**		**Total**	
	No	**%**	**No**	**%**	**No**	**%**
Hypertension	21	42	16	32	37	37
Kidney atrophy	7	14	7	14	14	14
Recurrent UTI	6	12	8	16	14	14
Obstructive Nephropathy	4	8	6	12	10	10
Hereditary	2	4	2	4	4	4
Antibiotic abuse	1	2	3	6	4	4

Diabetes mellitus	2	4	1	2	3	3
Unknown	7	14	7	14	14	14
Total	50	100	50	100	100	100

Table 3: The drug monitoring levels during this study:

Character	Cyclosporine group		Tacrolimus group		Total		P
	No	%	No	%	No	%	
Decrease	0	0	1	2	1	1	0.16
Normal	31	62	32	64	63	63	
Increase	19	38	17	34	36	36	
Total	50	100	50	100	100	100	

Table 4: The main effects of Cyclosporine and Tacrolimus in biochemical functions in a hundred renal recipients (Mean± S.D):

Character (normal range)	Cyclosporine group=50	Tacrolimus group=50	P
Sugar (3.05-6.38mmol/L)	5.39±1.67	5.6±2.1	0.581
Urea (1.5-8.3 mmol/L)	6.18±2.1	7.99±8.3	0.143
Creatinine (55-124 mmol/L)	113±32.5	116±74.4	0.761
T-bil (up to 18mmol/L)	14.8±7.8	9.4±5.7	<.0001*
D-bil (up to 5.1 mmol/L)	4.8±2.7	2.2±1.6	<.0001*
Got (up to 35U/L)	25.3±25.1	23.2±24.5	0.686
Gpt (up to 40 U/L)	35.3±46.4	24.9±17.1	0.139
Alk (35-129U/L)	112.5±45.9	98.4±42	0.112
GGT (5-61U/L)	59.8±72.2	29.1±11.4	0.004*

CHOL (up to 200 mg/dl)	209.2±47.4	144.1±39.8	<.0001*
HDL (>35 mg/dl)	42.3±12.0	34.7±5.2	<.0001*
LDL (<150 mg/dl)	128.3±36.7	81.8±31.5	<.0001*
TG (up to 200 mg/dl)	235.3±109.8	157.8±60.4	<.0001*

* significant

Table 5: The main effects of Cyclosporine and Tacrolimus in complete blood count "CBC" in a hundred renal recipients (Mean+ S.D):

Character (normal range)	Cyclosporine group =50	Tacrolimus group =50	P
Hb (115-180 g/l)	145.8±17.6	144.1±39.8	<.0001*
WBC ($4\text{-}10\times10^9$cell/L)	8.3±2.6	8.3±2.6	0.998
Plts ($150\text{-}400\times10^9$cell/L)	267.5±71.1	238.9±50.4	.023*

Table 6: The complications of Cyclosporine group and Tacrolimus group in a hundred renal allograft recipients:

Character	Cyclosporine group		Tacrolimus group		P
	No	%	No	%	
Gum hyperplasia	8	16	0	0	0.003*
Hairtusim	32	64	2	4	<.001*
Being diabetic	1	2	10	20	0.004*
Herpes zoster	5	10	0	0	0.001*
GITI	7	14	12	24	0.2
UTI	4	8	5	10	0.7
Couching face	11	22	0	0	<.001*
Fatigue	9	18	11	22	0.6

Kaposi sarcoma	1	2	0	0	0.15
Hair loss	0	0	10	20	0.001*
Polycythemia	0	0	1	2	0.3
Gastritis	2	4	5	10	0.23
Obesity	27	54	14	28	<.001*
Hypertension	12	24	5	10	0.09
Herpes simplex	14	28	3	6	0.003
No complication	6	12	4	8	0.5