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Original Article

The major causes of chronic and complication kidney disease and side effect of immune suppressive medications in Zawia patients kidney translation

Ebtesam A. Beshna[1], Abdurraouf M. M. Khalf[1], Abdurrahim A. Elouzi[2], Daniya A. Altarhouni[1], Anwaar N. Ashour[1], Zohra A.Saria[1], Shahrazad A. Eteer[3], Jamal A. Elbakay[3], Samar Benzaed[4].

1. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Zawia, Zawia, Libya
2. Department of Pharmaceutics, Faculty of Pharmacy, Tripoli University, Tripoli- Libya
3 . Department of Medicinal and Pharmaceutical Chemistry, Tripoli University, Tripoli, Libya
4. Department of Medicinal and Pharmaceutical Chemistry, Zawia University, Zawia, Libya

Abstract:

Identification of causes and complications of chronic kidney disease in patients on dialysis is essential for improving the quality of patients life. Immunosuppressive or immune suppressant drugs or anti-rejection drugs are employed to prevent different autoimmune diseases. The major side effects of these drugs are hypertension, hyperlipidemia, and hyperglycemia. 60 patients undergoing dialysis treatment for more than six months were studied in Zawia kidney hospital. The major cause of end-stage renal disease patients was non genetic (50%), genetic (41.7%), followed by unknown (8.3%). 50 patients for the maintenance immunosuppressive regimen of the study population mainly included Cyclosporine, and Tacrolimus. The result shown that, 45 patients had hypertension after kidney transplantation about 90% of all patients, followed by 34 patients had high level of cholesterol, while 31 patients had diabetes after kidney transplantation in this study, there for explain more the complication of immune suppressive drugs. Conclusion, The kidney failure patients is an incurable and continued progression disease that has dialysis as a treatment, or kidney transplantation, Finding All renal allograft recipients experienced are related to the adverse reaction. Prolongation of immunosuppressive treatment resulted in an increase in adverse drug reactions.

Keyword: Renal failure, kidney transplantation, cyclosporine, tacrolimus.

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Introduction

The function of the kidney is the filtration and secretion of the final products of metabolism and the excess of electrolytes. Chronic kidney disease is permanent failure of the kidney to accomplish its functions, and failure to sustain life, is called end stage renal disease (1). The most causes of chronic kidney disease are diabetic nephropathy, hypertension, glomerulonephritides, interstitial nephritis, pyelonephritis and polycystic kidney disease, (1). The process of dialysis helps in the removal of toxins from the body and slowly the kidney may regain its function that depends on the age and the health condition of the individual (2).

Therapeutic Drug Monitoring (TDM) is an integral part of therapy regimen to ensure effective pharmacotherapy of immunosuppressive agents of patients after organ transplantation (3,5). Tacrolimus and cyclosporine are examples of immunosuppression drugs which can be used for patients with cardiac transplantation. However, they are associated with a variety of side effects including diabetes (5,12). TDM is important in this case to determine the blood drug concentration that leads to the achieved clinical outcomes (1).

The multiple causes of post transplant hyperlipidemia have been reviewed in many studies. A genetic predilection has been shown to contribute to hyperlipidemia, but other factors such as level of diabetes mellitus, renal function, obesity, proteinuria, and some antihypertensive agents drugs are very significant, (6,7). Infrequently reported side effects of cyclosporine and tacrolimus are decreased kidney function, hepatitis, increased risk of infections, diabetes, increased cholesterol levels, sleep problems, headache, mild tremor, seizure, high blood pressure and others (8).

Tacrolimus is as an effective drug in preventing organ and tissue rejection after organ transplantation (9,13), however, its requires frequent monitoring and dose adjustments because of its metabolism and narrow therapeutic window even at low trough levels (4–6 ng/mL), It has been reported that nephrotoxicity is associated with the use of tacrolimus (9). Other side effects are related to the tacrolimus administration include reduction in renal blood flow and creatinine clearance, microangiopathic hemolytic anemia, hypertension, central-nervous-system demyelination and decrease in pancreatic insulin production (10).

Pharmacokinetics and Pharmacodynamics:

Tacrolimus and cyclosporine are given orally every 12 hours or as directed by doctor. The level of both drugs are tested regularly to ensure an adequate dose administered that prevent organ rejection and do not cause toxicity (13). The two drugs are highly lipophilic, therefore, they are poorly soluble and their bioavailability are generally poor with mean values around 25% (13).

Both drugs are metabolized by gastrointestinal CYP3A isozymes,

predominantly CYP3A4 and CYP3A5 (14) with less than 0.5 and 1%, respectively of the parent drug appearing unchanged in urine and feces. Approximately 95% of tacrolimus metabolites are eliminated through the biliary route with urinary excretion accounting for around 2% (15). P-glycoprotein also plays a major role in the pharmacokinetics of tacrolimus and cyclosporine which is encoded by the ABCB1 gene and it pumps xenobiotics from the cytoplasm to the exterior of the cell. It is available on the apical surface of cells and presents at high concentrations in the villus tip of enterocytes of the small intestine. The intracellular concentrations of both drugs are decreased by pumping them out of enterocytes into the intestinal lumen by P-glycoprotein. Variability in oral clearance of cyclosporine depends on variation in intestinal P-glycoprotein, where the higher levels of P-glycoprotein indicated a higher observed clearance of the drug (13).

Pharmacogenetics:

The main purpose of immunosuppressive therapy is to prevent graft rejection. So that the drug is to achieve the highest degree of immunosuppression and minimising toxicity or other adverse effects (16). Tacrolimus is calcineurin inhibitor and suppresses the activation, proliferation, and differentiation of T cells. Calcineurin inhibitors prevent the transcription of several cytokine genes involved in immune responses (16).

The initial dose administered is based on the patients' weight and age. The dose is adjusted that the blood drug concentration value should be within an acceptable range as the low dose could cause organ rejection whereas the high one could cause toxicity (16).

Mutations and polymorphisms of some genes (gene variations) that encode proteins involved in drug metabolism may affect the blood concentration of the pharmacologically active ingredient. The encoded proteins may affect drug metabolism by different mechanisms like by acting at intestinal absorption level and thus affect the amount of drug delivered to the bloodstream. In addition, they can influence the metabolism of the drug in the liver which subsequently can result in therapeutically inactive drug molecules. Finally, the encoded protein can modify the drug or its metabolites to facilitate their elimination from the body. Polymorphism of the encoded protein can lead to either increase or decrease its activity depending on the type of mutated gene. (16).

The aim of study:

The aim of the study was to identify the causes and complications of chronic kidney disease in patients on dialysis, and also to determine the common side effect or complications associated with the use of immune suppressive medications after renal transplantation at Zawia kidney hospital.

Materials and Methodology:

The study was carried out in Kidney hospital, which is the largest hospital in Zawia city –Libya. It established on February, 2014 with capacity of around 50 beds and the majority of the cases in this registry were from Zawia.

Cases identification and data collection:

This cross-sectional study was conducted on two groups of patients using census method. The first group of patients was those with renal failure and the second group was patients who had kidney transplantation with symptoms of complications from receiving immune suppressive drugs.

The dialysis center at this hospital has a team of doctors, nurses and nursing technicians who are responsible for performing the dialysis process and for maintaining the health status of the patient during the session.

The data collection process were obtained through face-to-face interview and also via reviewing the medical records of the patients. The study was focused on different the following parameters: sex, age, and cause of end-stage renal disease, presence or not of diabetes mellitus, hypertension, and level of cholesterol, (Table1).

The initial sample consisted of 60 patients who were on dialysis. The research included patients with over 10 years old (both genders) who had chronic kidney disease and on dialysis for more than six months.

All adverse reactions that occurred after starting immunosuppressive treatment were recorded by doctors. Reporting of side effects was based on face-to-face patient interviews at regular follow-up doctor visits. Additional information was also collected from the patients such as age, time of transplantation, immunosuppressive regimen and any co-administered drugs (name, dosage, frequency, indication, and route of administration).

Results

60 patients with end-stage renal disease were divided into three age categories; (10-30), (30-50) and (50-70) where the number of patients in each group was 4, 29 and 27 respectively as shown in Table 1.

Table 1: patients' age and number

Patient' age (years)	Number of patients
(10-30)	4
(30-50)	29
(50-70)	27

The history of genetic involvement was discussed with both patients and physicians as shown in (Table2).

Table 2: genetic history of the patients

The cases	Number of patients (female and male)
Genetic	25 (41.7%)
Non genetic	30 (50%)
Unknown	5 (8.3%)

A cross-sectional study was conducted for one month in 2021 on 60 patients of age 10-60 years old, who had kidney transplantation and received immunosuppressive therapy. Of these patients, 50 out of 60 were mainly receiving cyclosporine and tacrolimus (Table 3).

Table 3: Number of patients with age:

Age	10 – 30 years old	30 – 50 years old	50 – 60 years old
Number of patients	**6**	**20**	**24**

The major side effects namely hypertension, diabetes and cholesterol were reported for those 50 patients who were on immunosuppressive therapy as illustrated in Table

Table 3: Immune suppressive drugs with different side effects:

Side effect	Hypertension	Diabetes	Cholesterol
No of patients	45 patients	31 patients	34 patients

Out of 50 patients, 21 (42%) were on tacrolimus therapy. In this group, 7 patients (33.3%) had hypertension, 3 patients (14.3%) had both hypertension and cholesterol whereas 5 patients (24%) had diabetes and cholesterol. Finally 6 patients (28.6%) had hypertension, diabetes and cholesterol (Table 4).

Table 4: Tacrolimus patients with different side effects:

Tacrolimus (21 patients, 42%)	Side effects		
7 patients (33.3%)	**Hypertension**	-	-
6 patients (28.6%)	**Hypertension**	**Diabetes**	**Cholesterol**
5 patients (24%)	-	**Diabetes**	**Cholesterol**
3 patients (14.3%)	**Hypertension**	-	**Cholesterol**

The other group consisted of 29 (58%) patients who received cyclosporine therapy. 20 patients (69%) showed hypertension, diabetes, and cholesterol, while 9 patients (31%) had only hypertension.

Table 5: Cyclosporine patients with different side effects:

Cyclosporine (29 patients 58%)	Side effects		
20 patients (69%)	**Hypertension**	Diabetes	Cholesterol
9 patients (31%)	**Hypertension**	-	-

Discussion:

Optimal management of patients with chronic kidney disease (CKD) requires appropriate interpretation and use of the markers and stages of CKD, early disease recognition, and collaboration between primary care physicians and nephrologists.

In the present study 60 patients with End-stage renal disease patients were followed up for one week to evaluate co-morbidities that required hospitalization in association with epidemiological characteristics such as gender, age, diabetes, mode of dialysis and admissions in the hospital (a marker of overall morbidities or well being).

The present study showed that 25% of the participants perceived renal failure as a heavy burden in their life and they believed that nephropathy affected negatively their lives. This follows from

the fact that 10% of the respondents were feeling frustrated, were often feeling irritated trying to cope with their disease and while 50% used to spend a lot of time on each dialysis session. The great importance in the hemodialysis treatment, are social life and family relations. The disease influences and generates physical, social, psychological and emotional changes that often lead to the isolation of the patient and clinical depression,(18)

The social life and family relations are of great importance in the hemodialysis treatment, as the disease influences and generates physical, social, psychological and emotional changes that often lead to the isolation of the patient and clinical depression. Most chronic renal failure patient conducted with a research study was done before concerning depression in patients with 60% of the participants were feeling frustrated, since they were not as functional as they were before the initiation of dialysis, (17).

The time spent on dialysis was among the highest rated stressors for the participants, that because most of the patients receive haemo-dialysis three times a week and the majority of them spend four hours for each dialysis session. additionally to approximately 12 hours a week for dialysis, which is a significant amount of time for these patients (17).

Table (1) shows, increase the number of patients with increase of advancing age. The regulatory functions of the body gradually decrease, which describe the onset of chronic diseases in this stage of life, since over the years the body tends to lose gradually its regulatory functions, (18).

This study has 25 patients (41.7%), genetics with kidney failure disease, (Table 6) that have high blood pressure (hypertension). The most common causes for kidney failure disease are diabetes, high blood pressure, and glomerulonephritis, (19). The risk factor for end stage renal disease patients is hypertension and accounts for 27% of cases in the USA and 33.4% of end stage renal disease cases among African Americans, (20). There is an increase in the risk of end stage renal disease with increasing hypertension, (20).

The table (6) has been following about 6 patients, have high level of cholesterol that have the renal failure. This raises the possibility that one way to slow the onset of chronic kidney disease would be controlling a person's cholesterol levels. If kidney disease isn't slowed down or stopped, allot of people will need renal replacement therapy in the form of kidney transplantation or dialysis, (21).

Table 6: Shows the types of non genetics causes:

Non genetic	Hypertension	Cholesterol
30 (50%)	30	6

Five patients (8.3%) have end renal stage diseases with unknown causes (Table1). Epidemics of chronic kidney disease of uncertain etiology are occurring on the Pacific coast of Central America, Indian agricultural communities, in Sri Lankan, and in other hotspots around the world, (22).

21 (42%) patients use Tacrolimus and 29 (58%) use Cyclosporine after kidney transplantation in this study, and also they follow up every month with blood analysis in Zawia kidney hospital. For transplantation surgical techniques, better postoperative care, and effective immunosuppressive regimens all have contributed to prevent graft rejection and improve especially short-term and long-term survival rates, (22).

45 patients had hypertension after kidney transplantation about 90% of all patients, followed by 34 patients had high level of cholesterol, while 31 patients had diabetes after kidney transplantation in this study, there for explain more the complication of immune suppressive drugs, (Table 3). Hypertension is one of the most common clinical problems seen in kidney transplantation patients, and defined as the use of antihypertensive agents with or without elevated blood pressure (BP), has been reported to be as high as 85%, (25). Diabetes is a greater risk of fluctuating kidney function; therefore the management of diabetes mellitus in transplant patients is more challenging than the general population, (24).

Immunosuppressive therapy is associated with several long-term complications, such as hypertension, hyperlipidemia, osteoporosis, and diabetes mellitus. Furthermore, they can cause graft loss through direct nephrotoxicity, infection, malignancy, and no adherence to treatment. Therefore, having a comprehensive knowledge about the profile of immunosuppressive side effect in kidney transplant recipients has been recommended emphatically, (23).

From Table (4,5) show the different between two medicines (Cyclosporine and Tacrolimus) in side effects. Cyclosporine is more complication or side effect than Tacrolimus. 20 patients (40%) of Cyclosporine have hypertension, diabetes, and cholesterol, while only 6 patients (12%), have hypertension, diabetes, and cholesterol. Comparison studies of calcineurin inhibitors as immunosuppressant's in renal transplantation have demonstrated that Tacrolimus consistently reduces acute rejection rates and, in some studies, also improves long-term renal outcome in comparison to Cyclosporine, (26).

Conclusion:

The kidney failure patients is an incurable and continued progression disease that has dialysis as a treatment, which is a modality that requires discipline and also brings on several changes in the physical, psychological, social and environmental context, which influence the quality of life of patients. It is important to note that

even with these changes; dialysis is seen as a synonym of maintenance of life.

Finding All renal allograft recipients experienced are related to the adverse reaction. Prolongation of immunosuppressive treatment resulted in an increase in adverse drug reactions. Strategies such as continuous follow-up of patients, regular monitoring of Cyclosporine level and adjusting its doses with respect to monitoring findings, avoiding clinically significant interactions of immunosuppressants with other drugs, adopting much safer immunosuppressive regimens (e.g, Cyclosporine conversion to Tacrolimus), and educating patients could substantially decrease the rate of preventable immunosuppressive side effects among kidney transplant recipients.

Other healthcare professionals should be provide the Liquid chromatography–mass spectrometry (LC–MS) for all nephrology center, that provides a more accurate representation of the blood concentration of the parent compound Tacrolimus exclusive of metabolite, established cut points for Tacrolimus dosing may need to be adjusted to account for the increased risk of renal injury.

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