ABSTRACT BOOK

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Abstract

These are abstracts of the presentations made during the annual "RAK Update in Nephrology and Transplantation" held on the 19th and 20th of October 2012. Over 2 days, several renowned national, regional and international experts addressed topical issues in clinical nephrology, transplantation and related subjects such as cardiovascular risk, vasculitides and diabetes as they relate to kidney disease. These presentations covered a wide range of subjects addressing the latest basic research findings, clinical trial results and recommendations of the latest clinical practice guidelines. In addition, special attention was paid to adapt the research findings and international clinical practice strategies to local circumstances.

Key word: Chronic Kidney Disease, Diabetes, Lupus Nephritis, Systemic Lupus Erythematosis (SLE), Stem Cell, Transplantation

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with rising incidence prevalence. The annual "RAK Update in Nephrology and Transplantation" will be held on the 19 and 20th of October 2012. The meeting is jointly organized by RAK medical district, RAK Medical and Health Sciences University and Emirates Medical Association's Nephrology Section (EMA-N). Over 2 days, several renowned national, regional and international experts will address topical issues in clinical nephrology, transplantation and related subjects such as diabetes, cardiovascular risk and vasculitides as they relate to kidney disease. The advance abstracts of their presentations are produced here as they were provided in their original form par the minimal copyediting and

styling processes. It is hoped that by making them available online in *Ibnosinal Journal of Medicine and Biomedical Sciences* being an open access journal will serve very well the educational objectives of the event.

Abstracts of Presentations

SESSION I. Advancing Frontier in Nephrology and Transplantation

1.1 New Advances in IgA Nephropathy: The Absolute Renal Risk Concept and Recent Data on Autoantigen and Specific Autoantibodies.

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We have recently developed the new concept of "Absolute Renal Risk (ARR)" of dialysis/death in patients with IgA nephropathy (IgAN). This model allows accurate individual prediction of long-term prognosis in patients with IgAN, at time of diagnosis based on renal biopsy. It is based on three major and consensual risk factors: hypertension (HT), amount of proteinuria (g/d), and the severity of renal lesions on the biopsy. These independent factors were simplified and dichotomized: HT (yes or no); Proteinuria ≥1g/d (yes or no); and Global Optical Score (GOS) (0 to 20)≥8 (yes or no): the correspondence with Oxford classification is MEST (0 to 5) with a cut-off value of ≥2. The ARR is simply the count of these factors potentially present at diagnosis: 0, 1, 2, and 3. In a prospective cohort of 332 patients with IgAN, the cumulative incidence rate of Dialysis/Death 10 years after diagnosis was respectively 4% for ARR=0 (very low risk), 8% for ARR=1 (low risk), 18% for ARR=2 (high risk), and finally 68% for ARR=3 (very high risk) (1). The validation of this ARR is currently in progress.

Pathogenesis of IgAN has made significant progress. It is an immune complex disease. The auto antigen is the abnormal IgA, subclass 1, which exhibits a loss of terminal galactose in the lateral chains of the hinge region: the galactose-deficient IgA1. Consequently terminal GalNac molecules are exposed and become antigenic with specific antibody elicitation of both IgG and IgA isotypes: IgG-antiGlycans and IgA-antiGlycans. With the collaboration of J Novak (Alabama, USA) and H Suzuki (Tokyo, Japan), we have measured the serum levels of both the autoantigen and the autoantibodies in patients with IgAN, at time of diagnosis (renal biopsy). These biological markers are significantly elevated in IgAN versus controls (healthy and diseased). Moreover, there is a stepwise increment in these respective levels from ARR=0 to ARR=3. Finally, the serum levels of IgG and IgA autoantibodies associate with progression of IgA nephropathy (2). There are arguments to support the genetic basis of galactose-deficient IgA1. The mesangial transferrin receptor (CD71), the FcαR1 (CD89 on monocytes) and the transglutaminase 2 (TGT) molecules play an important role in the circulation and glomerular deposition of immune complexes in this disease.

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1.2 Kidney Transplantation: Current Concepts and Future Directions.

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Due to advancements in immunology and transplant surgery, short-term patients and graft survival have improved tremendously with more than 90% patient and graft survival at one year in many transplant centers in the USA. Unfortunately, the long-term outcomes

have remained unchanged during the last decade. Today, our challenges in kidney transplantation have changed compared to a decade ago. Acute cellular graft rejection is no longer our major concern, instead organ shortages, antibody mediated rejection, viral infections, medical issues and non-compliance have become our most important challenge in kidney transplantation. We are accepting more challenging and sicker patients that we did not accept ten or twenty years ago. The Organ shortage has become more prominent as our waiting list grows and more patients die while waiting for a kidney transplant. To tackle the new challenges a multidisciplinary team needs to be established. To overcome the organ shortage we increased the use of marginal organs by using dual kidney transplants. The long term outcomes of these organs in selected patients were very promising and were similar to standard criteria donors. To improve living donation, the paired exchange program shows a promising solution to transplant sensitized patients and increase living donation. Paired exchange results in better patient and graft outcomes and puts less financial burden on the transplant center. Currently, there is no reliable and easy test to gauge immunosuppression. It is clear that one size may not fit all. Some of our transplant patients may need more immunosuppression than others. To access the level of immunosuppression we studied the shift of NFKb in the CD3, CD4 and CD3, CD8 peripheral blood lymphocytes. The shift of NFKb from the cytosol to the nucleus was associated with rejection and viral infections. This test can be done in any given cell and has the potential to become an important test to gauge immunosuppression. Despite having more different immunsuppressive drugs than before, serious severe adverse effects still remain a challenge. Steroid and CNI withdrawal protocols were developed to reduce SAEs. In our randomized prospective study, we found that there was no benefit with steroid withdrawal. Patient, graft survivals, rejection rate and GFR remained equal in both steroid withdrawal and the control group but we observed more graft fibrosis in the steroid withdrawal group. In this randomized prospective trial we examined the effect of CNI withdrawal with protocol biopsy guidance. There was no effect of CNI withdrawal on the patient, graft survival and rejection rates. The Flowcytometry of the PBL shows that there was a better reestablishment of T-reg cells in the steroid withdrawal group but the recovery of T-reg cells was not associated with better short-term outcomes.

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1.3 Chronic Kidney Disease – Cardiovascular Disease: A Tight Link!!

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Chronic kidney disease (CKD) has reached epidemic proportions and is frequently under diagnosed & under treated. This is especially serious since CKD not only impacts patient outcome through progression to end stage renal disease but more importantly with increasing morbidity and mortality mainly related to cardiovascular disease. This is confirmed by a significant percentage of CKD patients succumbing to premature CV death making it the leading cause of mortality. Notably, CKD has also been classified as an independent risk factor for coronary artery disease (CAD), and together with albuminuria, are considered “CAD equivalent” based on common and nontraditional risks. Fortunately, there is mounting evidence supporting the strategy of “protecting the kidneys to save the heart”; data for which will be explored in this presentation. In addition the diagnostic difficulties of cardiac disease in CKD patients will be

discussed as it is frequently overlooked due to atypical presentation and difficulties in the interpretation of cardiac markers. This therefore, results in under treatment both medical and with invasive therapeutics which is in strict contrast to the needed early and aggressive treatment in this patient population. A high index of suspicion is thus required for early detection and appropriate treatment of CV disease in the setting of CKD, in addition to intensification of measures to halt CKD progression as well as particular attention to albuminuria along with other risk factors modification.

Further Readings

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1.4 The Chronic Kidney Disease Epidemic: Magnitude and Control Strategies

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Chronic kidney disease (CKD) is a worldwide public health problem with rising incidence prevalence. This increasing trend is expected to continue due to projected increases in diseases implicated in chronic kidney disease (CKD) development namely, diabetes and hypertension. Compounding this is the fact that a huge proportion of diabetic and hypertensive patients are either unaware or untreated, hence accelerating the renal insult. Moreover, obesity- metabolic syndrome is on the rise, this being an additional risk factor predisposing to CKD. All of this accounts for CKD reaching epidemic proportions which is a phenomenon seen in developed and developing countries. Unfortunately and as importantly, CKD is commonly under-diagnosed despite having significant societal impact. This is not only related to progression to end stage renal disease but also results in increasing morbidity and mortality with cardiovascular disease playing a leading role. It is not surprising then that lack of awareness for CKD and its risk factors results in lost opportunities for disease prevention. This is especially important given the mounting evidence for availability of measures to slow and even prevent progression, if CKD is detected in its earlier stages. This presentation will focus on raising awareness, early detection including who and how to screen, as well as therapeutic interventions as first line of defense against CKD epidemic.

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1.5 Pre Dialysis Clinic: The Tawam Hospital Experience

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Patients approaching kidney failure need optimized pre-dialysis care to improve their dialysis and transplantation outcomes. Lack of timely nephrologist input in the care of patients with progressive CKD has been demonstrated in several studies to be associated with poor clinical outcomes. The focus of 'late CKD' care has been expanded from planning of dialysis to all themes of the CKD action plan, including estimating and retarding progressive disease, preventing and treating complications, cardiovascular risk management, and, when possible, promoting pre-emptive transplantation. Management of severe CKD requires a well-organized patient-focused multidisciplinary team and early referral. In 2009, we have started at Tawam Hospital a pre-dialysis clinic aiming to improve the care of patients with advanced CKD (IV+V). We are reporting our 3 years experience, the characteristics of our CKD patients, the challenges and the outcomes.

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SESSION II. Clinical Practice Updates in Nephrology and Diabetes

2.1 Chronic Kidney Disease-Mineral and Bone Disorder: Pathology and Consequence

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Bone disease is traditionally referred as "Renal Osteodystrophy". However, disturbance in mineral and vascular calcification is not integrated in this bone disorder. Kidney disease: Improving Global outcomes (KDIGO) in 2009 described this disturbance as CKD mineral bone disorder (CKD-MBD). CKD-MBD is defined as systemic disorder of mineral and bone disease due to CKD manifested by one or more of following abnormalities in minerals (CA, PO_4, PTH or Vitamin D) or abnormality in bone Turnover (T), mineralization (M), volume (V) [which include linear growth, and strength] or vascular or other soft tissue calcification.

CKD-MBD starts early in CKD. In fact, high PTH was observed in 12% with eGFR value > 80ml/min/1.73 $m^{2.}$ Also, low serum Vitamin D was observed in 13% of patient with eGFR> 80ml/min/1.73m^2. However, serum $Ca^+ \alpha PO_4$ remained within normal unit till eGFR was less < 40 ml/min/1.73m^2. CKD-MBD is due to the continuous retention of phosphate brought by loss of renal mass, hypocalcemia, hypersecretion of FGF-23 and PTH, and reduction of 1,2,5 $(OH)_2D$. Later on, the retention of PO_4 and increase calcium phosphorus production will lead to vascular, valvular and soft tissue calcification. In fact, up to 44% of predialysis is CKD patient and up to 79% of dialysis patients has myocardial or visceral calcification. This calcification can cause arrhythmia, left ventricular dysfunction, valvular stenosis, ischemia, CHF and death. Prevention of CKD-MBD is essential to reduce cardiovascular mortality in renal patients. KDIGO and British Society

recommend to measure serum calcium, phosphate and PTH level when eGFR is < 60 ml/min/1.73m^2 (CKD, stage 3) and level of serum Ca and phosphate should be maintained within normal range. Further, intake increases PTH is recommended to be kept in high level of normal and if intake PTH persistent elevated then evaluation for hyperphosphatemia, hypocalcemia and vitamin D deficiency should be done and corrected. The treatment of mineral disturbance are composed mainly by restricted diet in phosphate, use calcium and non-calcium phosphate binder (Sevelamer, Lanthanum, MgCarbonate) and correct vitamin D in start from CKD stage 3 till stage 5. Even more aggressive removal of phosphate by increase dialysis is recommended to treat persistent hyperphosphatemia in dialysis patients. Since current approach for CKD-MBD is not optimal, researchers with continue to find the role of FGR-23 and better approach to inhibit absorption or transport of phosphate in gastrointestinal tract or renal tubules.

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2.2 Management of Lupus Nephritis

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Nephritis remains one of the most devastating complications and it is the major predictor of poor outcomes. Although the use of aggressive immunosuppression has improved both patient and renal survival over the past several decades, the optimal treatment of lupus nephritis remains challenging. Until recently, the treatment of lupus nephritis mainly rested on three drugs: corticosteroids, cyclophosphamide, and azathioprine. In the last decade, clinical trials have shown that less toxic drugs such as oral mycophenolate and are as effective for treating lupus nephritis. However, therapy for lupus nephritis has shown to be partially effective in terms of renal remission. Safer and more effective therapies are desperately needed to control disease activity and prevent organ damage. Directed target therapy against B and T cells could bring new insights for real effective treatment in lupus nephritis and thus achieving a better outcome in patients. Belimumab is a human monoclonal antibody that inhibits the biologic activity of human B lymphocyte stimulator; it has recently been approved by the FDA for lupus nephritis.

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2.3 Stem Cells Therapies for Type 1 Diabetes

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Current approaches aiming to cure type 1 diabetes mellitus (T1DM) have made a negligible number of patients insulin-independent. In this review, we revisit the role of stem cell-based applications in curing T1DM (1). A potential therapeutic approach for T1DM should preserve the remaining B-cells, restore B-cell function, and protect the replaced insulin-producing cells from autoimmunity (2). Stem cells hold immunological and regenerative properties that could be harnessed to improve the treatment of T1DM. By inhibiting T-cell function in the autoimmune response, stem cells re-establish peripheral tolerance toward B-cells thereby reverting diabetes (3). On the other hand, stem cell-derived insulin-producing cells are capable of engrafting and reversing hyperglycemia in mice (2). Bone marrow mesenchymal stem cells have a hypo-immunogenic phenotype and a wide range of immunomodulatory capabilities have been shown to cure new onset diabetes in NOD mice, and will be used in two imminent MSC-based trials (4). Cord blood stem cells have been shown to differentiate into glucose-responsive insulin-producing islet-like clusters and to facilitate the generation of regulatory T-cells reverting hyperglycemia in NOD mice (5). However, T1DM patients treated with cord blood stem cells did not show an improvement of glycometabolic control (6). Although hematopoietic stem cells have been used unsuccessfully in mice to revert hyperglycemia, they exhibited profound immunomodulatory properties in humans; indeed, newly hyperglycemic T1DM patients have been successfully reverted to normoglycemia with autologous nonmyeloablative hematopoietic stem cell transplantation (7). Finally, embryonic stem cells (ESCs) also offer exciting perspectives, as they are able to generate glucose responsive islet-like cells in vitro. Stem cells represent an unique therapeutic opportunity for type 1 diabetes.

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2.4 Patient-centered Approach for Management of Hyperglycemia in Type 2 Diabetes: An Overview of the Latest Guidelines.

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Over the last two decades. a significant expansion

occurred in the number of medications being available for management hyperglycemia in type 2 diabetes. This was coupled with major changes in our approach to diabetes management such as targets and need for individualization and the multiple risk factor modification. I was timely that the some guidelines were issued. They should help physicians effectively translate research into clinical practice. The newest guidelines on the management of hyperglycemia in type 2 diabetes were released by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in April of this year as their formally adopted position statement (1). These guidelines are different from the previously published guidelines (2). They introduced a non-algorithmic patient-centered approach that stresses the principles of individualization of care based on several important patients' attributes. They stressed the role of lifestyle modification as basic requirement, metformin as the first line pharmacological therapy and individually-tailored basis for the choice of the second and third line pharmacological treatment (3). The glucose control mega trials suggested that microvascular complications were reduced fairly readily in most of the studies whereas the reduction in macrovascular complications was not easily demonstrable (i.e. either not statistically significant) or needed longer time to become statistically significant).

The new guidelines emphasized that glycemic targets and glucose-lowering therapies must be individualized. Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. However, many physicians still support the notion that initiation of metformin at diagnosis is still their preferred option (if there is no contraindication). Limited comparative data exist to guide the choice of medication after metformin. Combination therapy with an additional one to two oral or injectable agents should follow and ultimately, many patients will require insulin therapy. The guidelines stress the fact that all treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, and needs. Notwithstanding that the main focus in these latest guidelines was hyperglycemia, the opportunity was not missed to stress the multiple risk factor modification lost to state that comprehensive cardiovascular risk reduction must be a major target of therapy. Physicians' inertia must be strongly discouraged and timely insulinization be considered early in the disease process.

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2.5 Blood Pressure Targeting in Type 2 Diabetes: Revisiting the Evidence.

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As an independent renal and cardiovascular risk factor, hypertension has a substantial impact on morbidity and mortality. In year 2001, the Global Burdon of Disease Study, worldwide mortality was analyzed. Out of 56 million fatalities, between 7 to 8 million could be attributed to arterial hypertension, supporting the notion that hypertension remains the most risk

factor. However it is import to note that absolute risk associated with high blood pressure is highly dependent on comorbidities. Diabetes, in this context, is a key factor to increase dramatically the risk for renal and cardiovascular events in hypertensive patients. That is why several guidelines have recommended goal blood pressure on treatment to be lower in hypertensive patients with Diabetes. However, strong evidence still lacking. The prevalence of diabetes in patients with hypertension is approximately twice in that with general population. On other hand, patients with diabetes exhibit high rates of hypertension ranging between 70-90%. Hypertension and diabetes, overweight/obesity are very prevalent comorbidities and underlying mechanisms have being identified which playing very important role. Hypertension may also be promoted by renal functional change, after the manifestation of diabetes. On the other hand, hypertension may further impair insulin sensitivity by microcirculation structural changes. For all that the blood pressure targets in type 2 diabetes need to be reviewed in evidence based way and more outcome studies need to limit or prevent the comorbidities and mortalities.

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2.6 Update on the Management of Diabetic Nephropathy

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Diabetic nephropathy is possibly the worst long-term diabetic complication and by far that one associated with the highest social and economic burden, being one of the main causes of end stage renal disease (ESRD) [1]. The overall risk of diabetic nephropathy in the population is not declining [1,2], despite improvements in glycemic and blood pressure control, and the introduction of renin–angiotensin system (RAS) blockers, thus rendering the quest for novel therapeutic approaches mandatory [3]. Two approaches can be used in this quest, the first one is to identify novel drug targets by gaining a better understanding of the pathogenesis of diabetic nephropathy at the molecular level [1,2], However, mounting evidence from human, animal, and *in vitro* studies indicates an alternative strategy, being that existing drugs, developed to treat other disorders, might also be effective in preventing or slowing the progression of diabetic nephropathy to end stage renal disease. The most obvious advantage of this approach is that clinical trials of these drugs, if justified, can be started at once. Examples of such drugs include the urate-lowering agent allopurinol, the anti-TNF agents etanercept and infliximab. Special consideration in the future treatment of diabetic nephropathy should be posed on the use of stem cell to repair the damage kidney tissue.

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2.7 Diabetic Complications and Uraemic Vasculopathy

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Diabetes mellitus represents a major health challenge for the 21st century, and its incidence is still rising. Diabetic nephropathy is a major chronic complication of diabetes with an adverse impact on morbidity and mortality (1). In the Western countries, Diabetes is among the leading causes of end-stage renal disease (ESRD) requiring dialysis (2). Vascular calcification is the dominant finding associated with calcific uremic arteriolopathy on tissue biopsy in patients with ESRD. Classically, the vascular pathology is characterized by small vessel medial calcification, intimal fibrosis and thrombosis, with necrosis of associated tissue (3). ESRD is associated with a significant increase in the frequency of diabetic foot lesions. This holds true for all foot complications, namely ulceration, infection, gangrene, and amputation, which are encountered at a more than twofold frequency in diabetic patients with ESRD as compared with their non-nephropathic counterparts. Tragically enough, the rate of amputations is 6.5–10 times higher among diabetic patients with ESRD in comparison to the general diabetic population (4). The increased incidence of diabetic foot complications is observed in all stages of diabetic nephropathy. Even as early evidence of nephropathy as microalbuminuria is an independent risk factor for foot ulcer (RR=8.2, $p < 0.0001$) (5). Coronary heart disease [defined as myocardial infarction, angina, and history of bypass surgery, percutaneous transluminal coronary angiography (PTCA) or pathology on coronary angiography] is frequently found in patients starting dialysis. The prevalence of coronary heart (in a national random sample of USA patients) disease was 38% and it was highly significantly more common in diabetic patients (46.4%) than in non-diabetic patients (32.2%). Much of the cardiac pathology is acquired prior to dialysis. This is documented by the high frequency of coronary lesions, i.e. 30–40%, which is found when diabetic patients undergo coronary angiography before they are put on the waiting list for transplantation (6). Much of the cardiac pathology is acquired even before the pre-terminal phase of renal. Disease is supported by the Canadian multicentre observation cohort where the prevalence of cardiovascular disease was 47%, independent of the severity of renal dysfunction. Progression, i.e. either new events or worsening of existing pathology, was seen in 20% of the patients over 23 months. The odds ratio for a new event in diabetic compared with no diabetic patients was 5.3 and this difference was highly significant (7). Special management care has to be given "for early intervention and prevention of all vascular complications" for diabetic patients as soon as they develop early diabetic nephropathy.

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SESSION III New Horizons in Transplantation Medicine

3.1 Current Status of Immune Suppression in Solid Organ Transplantation

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No Abstract Received

3.2 Polyomavirus Infection in Renal Transplant Patients

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Polyomavirus-associated nephropathy (PVAN) affects about 1-10% of kidney transplant recipients tending in a significant graft failure (up to 90%). Immunosuppression reduction is the corner stone in its treatment and addition of medications with anti-viral activity such as Leflunomide, Ciprofloxacin, intravenous Immunogloblulin (IVIG) and Cidofovir may enhance viral clearance and improve graft survival. Thirty patients were studied prospectively. They all had either early viremia or biopsy-proven (19%) or presumptive diagnosis of PVAN. They were divided into three groups according to the treatment given. Six patients (20%), with mean blood viral load of 230 copies/ml (range 149-400), had a median serum creatinine of 123 (range 68-218) umol/l at diagnosis and 104 (78-142) umol/l after 16 months (12-22) of follow up. They achieved complete viral clearance just with immunosuppressive therapy. Three patients (10%) received Ciprofloxacin; their mean viral load was 1,208 copies/ml (200-2850) and median serum creatinine was 135 (128-301) umol/l at diagnosis and 140 (126-365) umol/l after 16 months (4-24) of follow up. They had complete viral clearance. Twenty one patients (70%) were treated with Ciprofloxacin and Leflunomide and one patient received IVIG and Cidofovir additionally. Their median viral load was 3.2x104 (4x102-3.2x107) and the median serum creatinine was 127(68-218) umol/l at diagnosis and 135 (84-268) after 18 months (2-43) of follow up. Of these 7 patients cleared the virus, 13 patients had a significantly low viral load and 1 patient had a viral load of 3.4x104 after 14 months on treatment. There was no graft loss and no significant hematological and hepatic toxicity. One patient got pregnant six weeks after discontinuation of Leflunomide and gave birth to a healthy baby after 34 weeks of gestation. We conclude that in PVNP, Leflunomide and Ciprofloxacin are effectively enhancing viral clearance, although early detection of infection and reduction of immunosuppression remain the main stay of treatment.

3.3 How to Prolong Kidney Transplant? Long Term Outcomes

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Currently, the short-term outcomes of kidney transplantation are outstanding, with greater than 90% patient and graft survival at one year in a majority of transplant centers. Unfortunately, despite these lower rejection rates, the long-term outcomes remain unchanged. Many immunological and non-immunological factors may affect the long-term outcomes of kidney transplantation. Now we accept

sicker and older patients for transplant. Fifty eight percent of patients on the waiting list in the USA are >50 years old, 34% are African American and 17% need re-transplant. Patients with a history of cancer still can be candidates for transplant. Cardiovascular diseases are the major cause of patient death after kidney transplantation, followed by infection and malignancy. Therefore, our focus has shifted toward screening for CVD and careful monitoring of factors that may increase CV events following transplant. Controlling blood pressure >130, anemia (HB>10.5), hypercholesterolemia, post-transplant diabetes and control of blood sugar in the diabetic patients after kidney transplantation require multidisciplinary and diligent care. Weight gain and metabolic syndrome is not uncommon after kidney transplantation and requires a continuous team approach. Non-adherence also is one of the biggest challenges to many transplant centers. It is a complex, multi-factorial issue that cannot be easily predicted. Poor understanding of instructions and/or complicated regimens, adverse drug events, impaired access to therapy, psychosocial and socioeconomic factors may play a major role in non-compliance. Non-adherence can be difficult to measure. Most centers use patient self-reports, which may be inaccurate. The gold standard of assessing adherence is electronic monitoring of pill bottles. Practical strategies that may reduce or prevent non-adherence are to: educate the patient or caregiver on the importance of adherence, perform regular follow-up visits, provide transportation services if needed, address cost issues with patients, select an agent with limited or milder adverse effects and keep the immunosuppression regimen simple. The transplant team can play a significant role in early detection of non-adherence and motivate patients to adhere to a medication regimen by examining modifiable barriers to adherence and identifying solutions to overcome them.

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3.4 Islet and Pancreas Transplant in Type 1 Diabetes: Benefits and Novel Immunological Strategies

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Insulin represents a life-saving therapy for patients with type 1 diabetes but, despite appropriate treatment, it prevents only partially long-term diabetic complications, while generating fatal hypoglycemic episodes (1). Pancreas transplantation is a pretty well established procedure, which has been proven successful not only in reverting hyperglycemia but in abrogating the progression of diabetic complication as well (2). Islet transplantation gained attention because of its safety, effectiveness and minimal invasiveness, however it remains a procedure reserved for a selected group of patients (3). The introduction of the Edmonton Protocol in 2000, based on a newly designed steroid-free immunosuppressive protocol, revamped the course of islet transplantation (4). Islet transplantation has been demonstrated as a valid alternative to exogenous insulin treatment for type 1 diabetes, reducing the incidence and severity of diabetic complications. However, exhaustion of islet function and the side effects related to chronic immunosuppression limit this option to a few selected patients. Consequently, new and original immune-regulatory protocols have been developed. Particularly relevant is the attempt to develop tolerogenic protocols to avoid chronic immunosuppression. Several approaches have been

tested in a preclinical model, and some are now under clinical evaluation; the development of new small molecules and new monoclonal or polyclonal antibodies is continuous and raises the possibility of targeting new co-stimulatory pathways or depleting particular cell types (5). The use of stem cells has been tested both to take advantage of their immunological properties and to repopulate the recipient bone marrow with donor-derived cells. Treg generation has also been widely assessed. Xenograft islet transplantation, although having severe problems in terms of immunological compatibility could theoretically confer an unlimited source of donors; promising results have been shown by the use of donor pigs carrying human immune antigens (6). A completely different approach has been tested by the use of encapsulated islets; synthetic structures are used to hide islet alloantigen from the immune system, with preservation of islet endocrine function and nutrition. Once one of these strategies is demonstrated safe and effective, it will be possible to establish clinical islet transplantation as a treatment for diabetic patients long before the onset of diabetic-related complications.

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