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Nephrology and Organ Transplant Corner

Edited by Ahmed S Al-Arrayed*

Mycophenolate Mofetil (MMF) for Treatment Glomerulonephritis: A review of the Literature

Daniel Cattran, MD an international expert in the treatment of glomerulonephritis, reviewed the world's literature on the use of Mycophenolate Mofetil (MMF) to treat glomerulonephritis. He noted that MMF has multiple potentially beneficial effects. These include inhibiting proliferation of immune cells involved in glomerulonephritis, specifically B and T lymphocytes; inhibiting adhesion and migration of inflammatory cells to blood vessels; and induction of programmed cell death of inflammatory cells. Furthermore, MMF is likely to be highly specific for immune cells, there by limiting its side effects. The published literature testing MMF's effects in several published and unpublished clinical studies was reviewed. Dr Cattran emphasized that numerous studies suggest that MMF may be effective in treating a wide variety of renal diseases. However, he also reminded the audience that side effects could be significant, with many studies reporting infectious complications, most commonly herpes zoster, affecting approximately 20% of patients receiving MMF. Gl side effects are also common. Thus, although MMF may become an important new addition to the treatment of patients with glomerulonephritis, it should be used by those who are experienced with its indications, effectiveness and side effects.

Lupus Nephritis in Children

Another group of patients of particular concern is children with lupus nephritis. At the University of Miami, children with proliferative lupus nephritis who had WHO class III, IV or V+ lupus nephritis and who had been treated with IV cyclophosphamide in the past had only an approximately 28% chance of having still functioning Kidneys 5 years after their initial diagnosis. Although these results are discouraging, they are significantly better than the results seen before cyclophosphamide was first used, when essentially no patient had any functioning kidneys at that time. Nevertheless, more effective long-term therapies are needed.

Gesteira and colleagues reported their experience using MMF as maintenance therapy for children with lupus nephritis after the disease was controlled with IV cyclophosphamide. Relatively low doses of MMF, 300-600 mg/m^2, were used. Thirteen children have been treated with this regimen for at least 2 years. They observed that urine protein losses were improved after 18 months and that renal function, which typically worsened over time in patients not treated with MMF, tended to stabilize. In contrast to their previous findings, which indicated that only about 25% to 30% of children still had functioning kidneys after five years, approximately 75% of children treated with MMF had

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functioning kidneys after 5 years. In the University of Miami experience, MMF appears to be beneficial in the treatment of children with proliferative lupus nephritis. However, other centers treating children with lupus nephritis, but who do not use MMF, have reported outcomes similar to University of Miami experience. Clearly, additional studies are needed to define the role of MMF in the treatment armamentarium of children with lupus nephritis.

Liver Transplantation

Indication of liver transplantation and graft survival: The most frequent indications for liver transplantation is end stage chronic hepatitis and biliary cirrhosis in adults, biliary artesia and inborn metabolic deficiencies in children. These diseases cause chronic liver failure or an acute fulminate deterioration of the liver function followed by poor prognosis. One year patient survival rate is 80% in these categories of patients.

Donor selction and liver preservation: The liver of the cadaveric donor is matched by size and ABO-blood group to the recipient. Elevation of hepatic enzymes, hemodynamic instability or any other liver abnormalities excludes transplantation. Hepatic preservation time for successful transplantation is limited to approximately 16-24 hours. The incidence of a reduced or non-functioning organ increases with preservation time.

Transplant procedure: Liver transplantation is a difficult surgical procedure to perform and also requires non-surgical procedures. Recipient hepatectomy and orthotopic placement of the liver can lead to considerable blood loss and several episodes of hemodynamic instability which requires an excellent cooperation with the blood bank and the anesthesiology department. The transplantation is complete, if the anostomosis of supra and intra hepatic vena cava, portal vein, hepatic artery and biliary duct are connected. Split liver transplantation and living relatives as donors are also performed in more recent years to provide children with a reduced size graft. Results are equal to normal sized pediatric grafts.

Complications: Acute and chronic rejection occurs occasionally after liver transplantation. Intensive immunosuppressive therapy is attempted, but fulminant rejection or even chronic symptoms are refractory to drug management. Retransplantation is the mandatory treatment. Immunosuppressive therapy includes cyclosporine, corticosteroids and azothioprine in primary high dosage. Due to surgery, post surgical blood transfusions and immunosuppressive therapy, renal function often declines in the postoperative period. Hemodialysis can be essential.

Transplanted Skeletal Muscle Cells Restore Heart Function

Emma Hitt, PhD

ATLANTA (Reuters Health) Mar 05 – Skeletal muscle cell transplantation into the myocardium of heart failure patients appears to be safe and shows signs of efficacy, French researchers reported on Wednesday at the 6th International congress of the Cell Transplant Society.

In a phase –1 trial, Dr Jean Thomas Vilquin with the INSERM and University Hospital, Paris, and colleagues treated 10 male patients who had refractory chronic heart failure. The patients had a mean age of 60.3 years and New York Heart Association Functional

class-II-IV. The mean left ventricular ejection fraction (LVEF) was 24%, and all patients were candidates for coronary artery bypass grafting (CABG).

A muscle biopsy was taken from each patient. The cells were then processed and delivered by direct injection to the heart. The trial showed feasibility of cell production, tolerance of biopsy and injection, and indications of efficacy, including regional contractility and improvements in perfusion, Dr Vilquin reported.

Global left ventricular function increased significantly after transplant compared to baseline ($P<0.02$) and 14 out of 22 scarred cell transplant segments showed contractility after transplant compared with no contractility before transplantation.

"Our phase 1 trial indicates that it is possible to produce a large amount of cells in a short time course", Dr Vilquin told Reuters Health "that the injections and the biopsy are safe, and the first indications of efficacy are very promising".

Dr Vilquin noted during his presentation that the relative contributions of CABG and cell transplantation, the ultimate impact on quality of life, and the cause of arrhythmias are issues that still need to be addressed. Four patients experienced arrhythmias that were not anticipated during the study. "These can be controlled, and we have changed the design of the upcoming phase II study to account for this", he noted.

The first phase II clinical trial for this procedure is now underway. The study, to be sponsored in part by Genzyme Corporation, will aim to recruit 300 patients. The endpoints will be contractility of kinetic myocardial segments, major adverse cardiac events, left ventricular function, quality of life and dose effect.

"We are also looking at patients with other cardiomyopathies, such as dilated heart and pathologies not involving infraction", he added. So we may be able to enlarge the possible number of patients that may benefit from this procedure.

Islet Transplant Diabetes Complications, Perhaps Via C-Peptide Increase

Emma Hitt, PhD

ATLANTA (Reuters Health) Mar 04-in patients with type 1 diabetes who have had a kidney transplant, successful islet transplantation appears to improve long-term survival and endothelial function, as well as renal function, independently of improved glycometabolic control, according to new research.

Dr Antonio Seechi with the San Raffaele Scientific Institute, Milan, Italy and colleagues evaluated the long term effects of transplanted islets in diabetic macro/microangiopathy and renal function in 34 type 1 diabetic kidney transplant patients.

According to Dr Seechi, their findings suggest that adequate C-peptide levels may be more important than tight glycometabolic control in preventing the late complications of type 1 diabetes. Although the mechanism is unclear, the findings support the idea of using C-peptide to help prevent metabolic complications, he told Reuters Health.

The researchers presented the findings on Monday at the 6th International Congress of the cell Transplant Society here in Atlanta, Georgia.

Patients were divided into those who had undergone successful islet transplantation, defined as those having a fasting C-peptide serum concentration of more than 0.5ng/ml for more than one year (n=21); and those who had an unsuccessful islet transplantation denoted by a lower C-peptide level (n=13).

Of the successfully transplanted patients, 90% were still alive at year 7 compared to only 51% of the patients for whom the islet cell transplantation was unsuccessful (p=0.04), the researchers report.

The successful group also experienced a lower cardiovascular death rate of 1/21 patients compared to 4/13 patients in the unsuccessful group (p=0.04) and slower intima media thickness progression (p=0.03).

Markers of endothelial function were also better in the successful group. These patients had a higher level of endothelial dependent dilation (p=0.02), higher basal nitric oxide levels (p=0.02), and lower levels of von Willebrand factor (p=0.02) and D-dimer fragment (p<00.01) compared to the unsuccessful group.

During the same session, Dr Seechi also presented 4 year data regarding renal function from the same patients. Natriuresis decreased, Na+-K+-ATPase immunoreactivity increased, and red blood cell activity increased in the successful islet transplant group compared to the unsuccessful group, where as microalbumiuria increased in the unsuccessful group.

Dr Seechi noted that these findings might also hold true for diabetic patients who have not undergone kidney transplant.

"Glycometabolic control is a good target, of course", Dr Seechi said, "but it is not required to improve late complications of diabetes".

> "Several companies are trying to synthesize endogenous C-peptide treatment", he noted. "The next step will be to investigate the mechanism further, to see if it is truly C-peptide dependent or not".