

The History Of Liver And Renal Transplantation

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Abstract

The Shiraz Nemazi transplant centre was the pioneer transplant unit of Iran, which performed the first kidney transplant in 1967 by Ghods and the first liver transplant by Malek Hosseini in 1995 (1,2). In this article we review the history of both, liver and renal transplantations.

THE HISTORY OF LIVER AND RENAL TRANSPLANTATION

Historically, in ancient civilizations, man had already imagined changes in the morphology, structure and function of the human body. Egyptian and Greco-Roman mythology provides us with countless examples of the metamorphoses sung by Homer and Ovid, symbolic incarnations of the “comédie humaine” with its strength, weaknesses, vices and virtues.

The liver has been the noble organ, the organ of life from time immemorial - liver in English, Leber in German, derived from the verb to live. Shakespeare a faithful interpreter of ancient traditions places the liver in first position in his famous list:

“Liver, brain and heart these sovereign thrones” (Twelfth Night, Act 1, Scene 1).

The current status of liver transplantation as a realistic treatment for acute and chronic end-stage disease has been long-awaited. Mythical literature richly describes transplantation as a cure for disease. Subsequently, in modern times, replacing a diseased organ with a healthy one from another individual, dead or alive, to enable a human to survive, can be considered to be the most stirring event in the field of medical science. An Indian legend from the 12th century B.C. recounts the powers of Shiva, who xenotransplanted an elephant head onto a child to produce the Indian god Gaesha (3). In ancient China, Yue-Jen (407-310 B.C.) induced anaesthesia lasting 3 days by “the absorption of extremely strong wine, opened up the chest of two soldiers and after examining them, exchanged their hearts and transplanted them”.

The first reference to the concept of organ transplantation and replacement for therapeutic purposes appears to be to Hua-To (136 to 208 A.D.) who replaced diseased organs with healthy ones in patients under analgesia induced with a mixture of Indian hemp.

Tissue grafting began in plants and until the 12th century this technique was referred to by the word “grief”, derived from the Greek word for stylet, the tool used to perform the operation. Although attempts were made to transplant every type of organ in animals, very rapidly the kidney was adopted as the experimental model because of its bilateral nature and the large calibre of its vessels with a well isolated pedicle (4).

Liver transplantation was first attempted in dogs by Welch in Albany in 1955 and Cannon in California in 1956 (5). The first liver transplant in humans was performed on March 1, 1963 by Starzl in Denver (6). The three-year-old child with biliary atresia, in a disastrous physiological condition, received the liver from another child who had died from a brain tumour. The recipient survived for five hours after the transplantation, succumbing to the complications of coagulation and haemostasis encountered during the operation. The second liver transplant in man was performed on May 5, 1963, was more successful, although the patient died on the 22nd postoperative day from pulmonary embolism but with a normal liver. The first long-term survival was achieved in 1967 by Starzl. Continuing progress in the 1960's and 1970's was very slow and one year patient survival was only 35 %. The 1980's was a decade in which new immunosuppressive therapies after liver transplantation helped to increase graft and patient survival by treating acute and chronic rejection more

effectively. One year survival for liver transplantation in Europe rose progressively from 47 % (1968-1988) to 67 % (1988-1996). A further advance was the improvement of liver preservation by the introduction of University of Wisconsin Solution (Viaspan) in 1987 extending periods of cold storage in Collins solution by two to three fold (7,8).

Jaboulay performed the first renal transplant in man, transplanting the left kidney of a pig, into the left elbow of a woman suffering from nephritic syndrome (9). Like other subsequent attempts the graft failed rapidly because of vascular thrombosis. Not until 1954, was it shown that a denervated kidney could function normally when reimplanted in the same person from whom it has been taken. In 1936, the first human cadaveric renal transplant performed by Voronoy in Russia, survived four days and due to genetic incompatibility between the donor and the recipient, homologous transplantation seemed doomed to failure (10). Renal transplantation between monozygotic twins confirmed the necessity of genetic identity and led to a realisation of the need for immunosuppression in prolonging graft survival (11).

GRAFT REJECTION

Rejection can be defined as graft damage arising from response to the transplanted organ by the recipient immune system and may take several forms resulting in different clinical patterns (12). The two major presentations after liver transplantation are acute and chronic rejection, with hyperacute rejection rarely encountered. Acute rejection may occur at any time after liver grafting with the first episode usually occurring around the 7th day (13). The diagnosis, suggested by clinical signs and biochemical abnormalities, is confirmed by histology. Three fundamental histological lesions are usually observed: a portal infiltrate of inflammatory cells, biliary lesions and endoheliitis (14, 15).

Chronic rejection, which can present as early as the first two weeks after transplantation, is characterised by slowly declining graft function and is usually accompanied by the corresponding elevation of liver enzymes and especially bilirubin (16,17). Histological changes include a progressive reduction in the number of bile ducts associated with the classical histological picture of “vanishing bile duct syndrome” and the thickening of the hepatic arterioles and obliterative arteritis (18). Medawar was the first to assert that rejection was an immunological response, with the inflammatory reaction due to lymphocyte infiltration. Sophistication of the initial immunological concepts resulted

from diverse observations including those that: (a) a second graft from the same donor to the same recipient was destroyed more quickly than the first; (b) a second graft from a different donor was usually treated like a first graft; (c) grafts between non-identical twins were accepted as well as those between identical twins; (d) the injection of tissue from one mouse strain into the embryos of another and the ability of the foetus to survive suggested that injected tissue contained lymphoid cells that could react against the defenceless host causing “graft versus host disease” (19). These preliminary indications suggested that the tendency to reject grafts might be overcome.

IMMUNOSUPPRESSIVE AGENTS

Although the results obtained with total body irradiation represented a considerable advance, its extreme severity resulted in a high mortality rate from aplasia. The anti-metabolite drug 6-mercaptopurine, which is structurally akin to adenine precursors, was used by Schwartz and Damashek in 1959. They found it competitively inhibited multiple steps in the de-novo and salvage pathways of purine synthesis and prevented rabbits from producing antibodies to foreign protein (20). By protecting the free mercapto group of 6-mercaptopurine from gut hydrolysis by production of its nitroimidazole derivative, azathioprine, it was possible to augment the activity of enteral 6-mercaptopurine and prolong kidney graft function in dogs (21).

Azathioprine was then used in transplantation but its low efficacy was associated with considerable myelotoxicity. Following observation by Goodwin that cortisone could reverse the acute rejection of renal allografts the combination of azathioprine and cortisone was used clinically to optimise benefit and reduce toxicity. The most widely evaluated and promising currently are cyclosporin, tacrolimus (FK506) mycophenolic acid mofetil, sirolimus (rapamycin), mizoribine, deoxyspergualin, brequinar sodium, leflunomide and monoclonal antibody preparations (22).

Mycophenolate Mofetil (MMF) was approved for use in 1995, in combination with cyclosporin and prednisone, in preventing rejection in renal transplant patients. MPA selectively and reversibly inhibits inosine monophosphate dehydrogenase (IMPDH), an enzyme that plays a pivotal role in synthesis of new DNA (23). Sirolimus (rapamycin) impedes progression through the G1 transition of the proliferation cycle in IL-2 stimulated T-cells, resulting in a mid-to-late G1 phosphorylation/activation of the P70S6 kinase (P70S6K), an early event of cytokine-induced

mitogenic response. By inhibiting this enzyme, whose major substrate is the 40S ribosomal sub-unit S6 protein, rapamycin reduces the translation of certain mRNA encoding for ribosomal proteins and elongation factors, thereby decreasing protein synthesis. A second, later effect of rapamycin in IL-2-stimulated T-cells is an inhibition of the enzymatic activity of the cyclin-dependent kinase cdk2-cyclin E complex, which functions as a crucial regulator of G1 transition. This inhibition results from a prevention of the decline of the p27cdk inhibitor, that normally follows IL-2 stimulation (24, 25). Sirolimus has been shown to be efficacious alone or in combination with other immunosuppressive drugs, such as cyclosporin, in prolongation of renal-allograft survival. A relationship between trough concentrations of sirolimus and graft outcome has been shown in both animal and clinical studies (26).

The introduction of cyclosporin for immunosuppression in liver transplantation in the early 1980s heralded a new age for transplantation. Its efficacy allowed rapidly expanding indications within and outside transplantation and permitted both the relaxation of restrictions in donor selection as well as in the preservation of grafts. Liver transplantation together with that of other organs (kidney, pancreas, heart, heart-lung, intestine), became possible (27).

In T-cells cyclosporin inhibits the calcium/calmodulin-dependent phosphatase calcineurin thereby preventing the activation of T-cell specific transcription factors such as NF-AT involved in lymphokine gene expression (28, 29). Oral cyclosporin therapy was complicated by inconsistency in the absorption of the conventional formulation (Sandimmun), particularly in liver transplant recipients (30, 31). A considerable reduction in this variability was achieved following introduction of a microemulsified formulation Neoral in the mid 1960's (32,33). Additional comparisons of Neoral with Sandimmune in both volunteers and liver and renal graft recipients have demonstrated a better correlation of AUC measurements with trough levels, a greater independence of absorption on and a greater consistency of absorption profiles (34). Monitoring of cyclosporin concentrations in blood is an invaluable and essential aid in adjusting dosage to ensure adequate immunosuppression while minimising toxicity. Cyclosporin is extensively metabolised to more than 25 metabolites (34) with cytochrome P450 3A4 iso-enzymes located in liver and small intestine mainly responsible and implicated in several drug interactions (35). Liver dysfunction leads to an alteration

of the metabolite patterns and to increased concentrations of cyclosporin metabolites in blood (36) but renal failure was shown not to affect the elimination of cyclosporin and little cyclosporin was removed from the body by hemodialysis (37).

Tacrolimus (FK506, prograf) was first isolated from the culture broth of a soil sample "Streptomyces tsukabaensis" from the tsukuba area in northern Japan by Kino et al (38). Because of its narrow therapeutic range and variable pharmacokinetics (39), tacrolimus requires therapeutic drug monitoring. Tacrolimus inhibits lymphocyte pathway in both CD⁺ and more markedly, CD⁺ T-cells by forming pentameric complex with its binding protein, calmodulin, calcium and calcineurin, so inhibiting the phosphatase activity of calcineurin and the dephosphorylation of transcription factors (40). After liver transplantation, the indication for transplantation (i.e., acute or chronic liver failure) appears to be a major determinant of variability in tacrolimus pharmacokinetics (39).

Postoperative ileus and decrease in intestinal permeability induced by tacrolimus may contribute to this variability (41). The influence of these variables could be predicted from regression models, which may be valuable for individualising tacrolimus dosage after liver transplantation (39). Alternative measurements of tacrolimus related activity could be made in patients' blood samples using a pentamer formation assay (42).

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