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Nephro and neurotoxicity of calcineurin inhibitors and mechanisms of rejections: A review on tacrolimus and cyclosporin in organ transplantation

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ABSTRACT

Context: In the meadow of medical sciences substituting a diseased organ with a healthy one from another individual, dead or alive, to allow a human to stay alive could be consider as the most string event. In this article we review the history of transplantation, mechanisms of rejection, nephro-neurotoxicity of tacrolimus and cyclosporin in organ transplantations.

Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science have been searched.

Results: 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. In 1936, the first human renal transplant performed by Voronoy in Russia. The first liver transplant in humans was performed on March 1, 1963 by Starzl in Denver, USA. Medawar was the first to assert that rejection was an immunological response, with the inflammatory reaction due to lymphocyte infiltration. Consequently, rational immunosuppressive therapies could inhibit deleterious T-cell responses in an antigen specific manner.

Conclusions: Searching related to the history of organ transplantation from mythic to modern times suggests that, to prevent graft rejection, minimize nephro and neuro toxicity monitoring of immunosupressive concentrations could provide an invaluable and essential aid in adjusting dosage to ensure adequate immunosuppression.

Review Article

Implication for health policy/practice/research/medical education:
Previous studies from the 12-th century B.C. up to modern times have focused on quality and quantity of life in transplant recipients. This review focuses on the history of transplant and immunosuppressive drug therapy.

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1. Context

The introduction of cyclosporin and tacrolimus for immunosuppression in organ transplantation heralded a new age for transplantation. The efficacy of both drugs 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. Mythical literature richly describes transplantation as a cure for disease. 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. 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.

Transplant antigens must be efficiently presented to the recipient's immune system to evoke a rejection response. The host immune system must recognise an allograft as being foreign before it can mount an immunological reaction against it. The human major histocompatibility complex (MHC) is referred to as the HLA complex and comprises seven genetic loci clustered on the short arm of chromosome 6 (1-4).

In this article we review the history of transplantation, mechanisms of rejection, nephro-neurotoxicity, of tacrolimus and cyclosporin in organ transplantations.

2. Evidence Acquisition

Directory of Open Access Journals (DOAJ) Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science were searched with key words relevant to "Immunosuppression, Mechanisms of Rejection, Toxicity, Organ Transplantation".

3. Results

53 research and review articles relevant to this topic directly or indirectly have been found. From the information given in these papers, the following aspects were drawn out.

3.1 The History of Organ Transplantation

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.

Jaboulay (1,2,5) 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 (1,6). Like other subsequent attempts the graft failed rapidly because of vascular thrombosis. Until 1954, it was 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 (1,7-8).

Liver transplantation was first attempted in dogs by Welch in Albany in 1955 and Cannon in California in 1956. The first liver transplant in humans was performed on March 1, 1963 by Starzl in Denver (9). The recipient survived for five hours after the transplantation, succumbing to the complications of coagulation and haemostasis encountered during the operation. The first long-term survival was achieved in 1967 by Starzl (1). 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% in 1968-1988 to 67 % in 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 (1, 10, 11).

3.2 Mechanisms of 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 (12-14). The two major presentations after liver transplantation are acute and chronic rejection, with hyperacute rejection rarely encountered (15,16). Acute rejection may occur at any time after liver grafting with the first episode usually occurring around the 7th day. 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 endotheliitis (17). 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. 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 (1, 9). Graft rejection may be governed in part by the type and extent of histocompatibility differences between donor and recipient with humoral mechanisms of likely greater importance in the rejection of renal than liver grafts (1, 12, 19). The two principal events of the human immune response are the recognition of epitopes on peptide antigens by T-cell receptors (TCR) and recognition of different epitopes on processed antigens by B-cell receptors. These initial events result in cytokine-dependent proliferation, differentiation and maturation of functional subsets of T-cells and B-cells that secrete immunoglobulin (1, 20, 21). These cytokines not only serve as ligands for cellular receptors that generate and regulate the immune response, but they may also be toxic to adjacent cells or tissues. Adhesion molecules present on leukocytes and target tissue regulate migration of effector cells and their adherence to antigen-presenting cells (APCs) or target cells expressing foreign antigens. Transplant antigens must be efficiently presented to the recipient's immune system to evoke a rejection response (1, 21, 22).

This may occur in one of two ways: (a) donor antigen may be processed by host APCs and presented in conjunction with host class II histcompatibilty antigens; (b) donor antigen can be presented directly to alloantigen-specific host cells by donor APCs without the need for processing by the host for host class II restriction (1). Numerous cells can function as APCs, including Kupffer cells, macrophages, dendritic cells, endothelial cells, B-cells and activated T-cells. Processing and release of an antigen by an APC or degradation of antigen by extracellular proteases in sites of inflammation may produce exogenous peptides (1, 23).

Cytokines are soluble proteins secreted by multiple cell types (monocytes, macrophages, lymphocytes, endothelial cells and fibroblasts) that regulate the immune response. Soluble factors, cytokines and arachidonic acid metabolites may exacerbate graft damage. Tumor necrosis

factor, which is produced by activated macrophages, has cytotoxic properties. Activation of macrophages or dendritric cells results in production of interleukin-1 (IL-1), which stimulates the production of IL-2 by antigen-stimulated CD4+ T-cells. IL-2 binds to IL-2 receptors on antigen stimulated precursors of helper, cytotoxic, and suppressor T-cells, resulting in their proliferation. The diverse effects of these cytokines may magnify effector mechanisms in allograft rejection. The development of acute rejection in liver transplantation may occur as follows: (a) APCs (which may include biliary epithelial cells and vascular endothelial cells) present transplant antigens to CD4+ T-helper cells in the presence of interleukin 1; (b) these T-cells become activated and release lymphokines (including interleukin 2) which lead to the recruitment and proliferation of lymphocytes, some of which have cytotoxic potential; (c) the escalating immunological reaction results in the production of cytokines which attract other cell types such as eosinophils, macrophages and neutrophils; (d) the combination of T-cell cytotoxicity and a more generalised inflammatory response results in damage to the graft and finally clinical rejection (24, 25).

The host immune system must recognise an allograft as being foreign before it can mount an immunological reaction against it. Recognition depends on the presence of allogeneic histocompatibility determinants and the most important of these are coded for by the major histocompatibility complex (26, 27). The function of major histocompatibility antigens is to act as recognition signals in lymphocyte reactions. They are essential for the development of both humoral and cell-mediated responses and are involved in recognition of self (1,28). The human major histocompatibility complex (MHC) is referred to as the HLA complex and comprises seven genetic loci clustered on the short arm of chromosome 6 (1, 24, 27). The HLA gene products are subdivided on the basis of their function and biochemistry into class I and class II. Class I MHC molecules are required for antigen presentation to CD8+ T-cells, can be recognised directly as antigen presentation to CD4+ T-cells and are also potent allogeneic antigens. Class I MHC molecules can bind endogenous peptide antigens, antigenic proteins from infectious agents and autoantigens. In contrast, class II MHC molecules bind only processed peptide fragments of antigen. T-cells expressing the cell-surface molecule CD8+ preferentially recognise antigen-MHC class I complexes whereas T-cells bearing CD4+ antigens preferentially recognise antigen-MHC class II complex. CD8+ and CD4+ T-cells can also react directly with allogeneic (non-self) MHC molecules. The summation of these points confirms Medawar's hypothesis that non-self class I and class II MHC antigens are recognised as foreign following allograft transplantation (1, 28,29).

3.3 Imunosuppressive therapy (Tacrolimus and Cyclosporin)

A major objective of rational immunosuppressive therapies is to be able to inhibit deleterious T-cell responses in an antigen specific manner (1, 29-31). Peripheral deletion of activated T-cells has an important function in the regulation of the extent of an immune response. Agents, which attack T-cells are associated with profound immunosuppression i.e., T-cell selective pharmacological agents primarily inhibit elements that regulate their maturation or differentiation. The prototypes of this family of agents are cyclosporin and tacrolimus, which inhibit antigenic signal activation necessary for lymphokine synthesis and cytotoxic T-cell generation. (1, 32, 33). Combination of total body irradiation, adrenal cortical steroids, and the myelotoxic drug 6-mercaptopurine (6-MP), were shown between 1953 and 1959 to modestly prolong skin allograft survival in several animal species (34). Although the results obtained with total body irradiation

represented a considerable advance, its extreme severity resulted in a high mortality rate from aplasia (1, 34).

Azathioprine was 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 (1) the combination of azathioprine and cortisone was used clinically to optimise benefit and reduce toxicity (1, 35).

The major advance in clinical immunosuppression eventually arrived in 1983 with the introduction of cyclosporin. Trials with the first of the new generation of primary immunosuppressants, tacrolimus (FK506) began six years later and were followed by a continually growing series of new agents. The most widely evaluated and promising currently are mycophenolic acid mofetil, sirolimus (rapamycin), mizorbine, deoxyspergualin, brequinar sodium, leflunomide and monoclonal antibody preparations (1, 36, 37).

Mycophenolate Mofetil (MMF), the morpholinoethyl ester pro-drug form of mycophenolic acid (MPA), 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. IMPDH is the first of two enzymes responsible for the conversion of inosine monophosphate to guanosine monophosphate and activated T-cells are exquisitely dependent on this pathway for synthesis of new DNA (36-38).

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 and intestine), became possible. 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 lymophokine gene expression (39). Oral cyclosporin therapy was complicated by inconsistency in the absorption of the conventional formulation (Sandimmun), particularly in liver transplant recipients (40).

4. Conclusions

In this review the history of organ transplantation, mechanisms of rejection and immunosuppressive therapy related to both tacrolimus and cyclosporine have been summarized. It could be concluded that immunosuppressive monitoring to prevent graft rejection and nephro-neurotoxicity is an invaluable and essential aid in adjusting dosage to ensure adequate immunosuppression. Cyclosporin is extensively metabolised to more than 25 metabolites with cytochrome P450 3A4 iso-enzymes located in liver and small intestine mainly responsible and implicated in several drug interactions (41- 44).

Tacrolimus inhibited thymocyte differentiation, T-cell proliferation and cytokine production with additional inhibition of B-cell activation and proliferation also noted. Tacrolimus binds first to an abundant, endogenous cytosolic 11.8-kDa protein termed FK506-binding protein (FKBP). It forms a pentameric complex with calcineurin, calmodulin and calcium. Dosage may also vary with the indication for transplantation and the time after grafting. Liver transplant recipients' show reduced demands for tacrolimus with increasing time after grafting and paediatric recipients require larger doses because of increased clearance.

Many of the toxic effects of tacrolimus are more frequent after intravenous than oral administration and may be reversed on dosage reduc-

tion. Toxicity may occur more frequently in liver graft recipients early after transplantation when serum albumin and plasma protein binding are low, increasing free drug concentrations. Because of the continued reductions in tacrolimus dose, there has been a considerable decrease in the frequency of severe adverse reactions, but the major manifestations continue to be nephrotoxicity, de-novo diabetes mellitus, infections and a broad range of neurotoxicities (1, 45, 46).

Cyclosporin and tacrolimus appear to induce a similar incidence of nephrotoxicity, and similar changes in serum creatinine levels occur with either drug following transplantation. The clinical presentation and morphology of tacrolimus nephrotoxicity are identical to those of cyclosporin. The exact mechanism of tacrolimus nephrotoxicity remains unknown but may result from alterations in mesangial and endothelial cell production of vasoactive substances which are a contributing factor to the decreased renal blood flow and glomerular thrombosis. In liver transplant recipients no convincing therapeutic strategies exist to combat nephrotoxicity other than dose reduction. The nephrotoxic potential of tacrolimus is markedly enhanced by ischaemia and other nephrotoxic drugs.

Tacrolimus has a negative effect on the pancreatic beta islet cell. Glucose intolerance and diabetes mellitus are well recognised complications of tacrolimus-based immunosuppression among adult solid organ transplant recipients but may be confounded by the influence of preoperative events in the short term.

Infections with bacterial, fungal, viral and protozoal organisms were reported to occur in less than 50% of patients treated with tacrolimus. A retrospective analysis of 2180 liver transplant recipients showed that the incidence of aspergillosis was significantly lower among patients receiving tacrolimus than cyclosporin. Infections, and particularly those with cytomegalovirus, were less frequent in acute liver failure patients after liver transplantation and receiving immunosuppression with tacrolimus versus cyclosporine. Post-transplant lympho-proliferative disorders (PTLD) occur with a similar incidence among patients treated with either tacrolimus or cyclosporin. However, there is a strong association between the development of PTLD and infection with Epstein-Barr virus (EBV) especially in children treated with tacrolimus.

The broad range of nervous system disorders most frequently encountered includes tremors, headache and insomnia, with other less common manifestations including paraesthesia and seizures (1, 47-53).

Conflict of interest

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