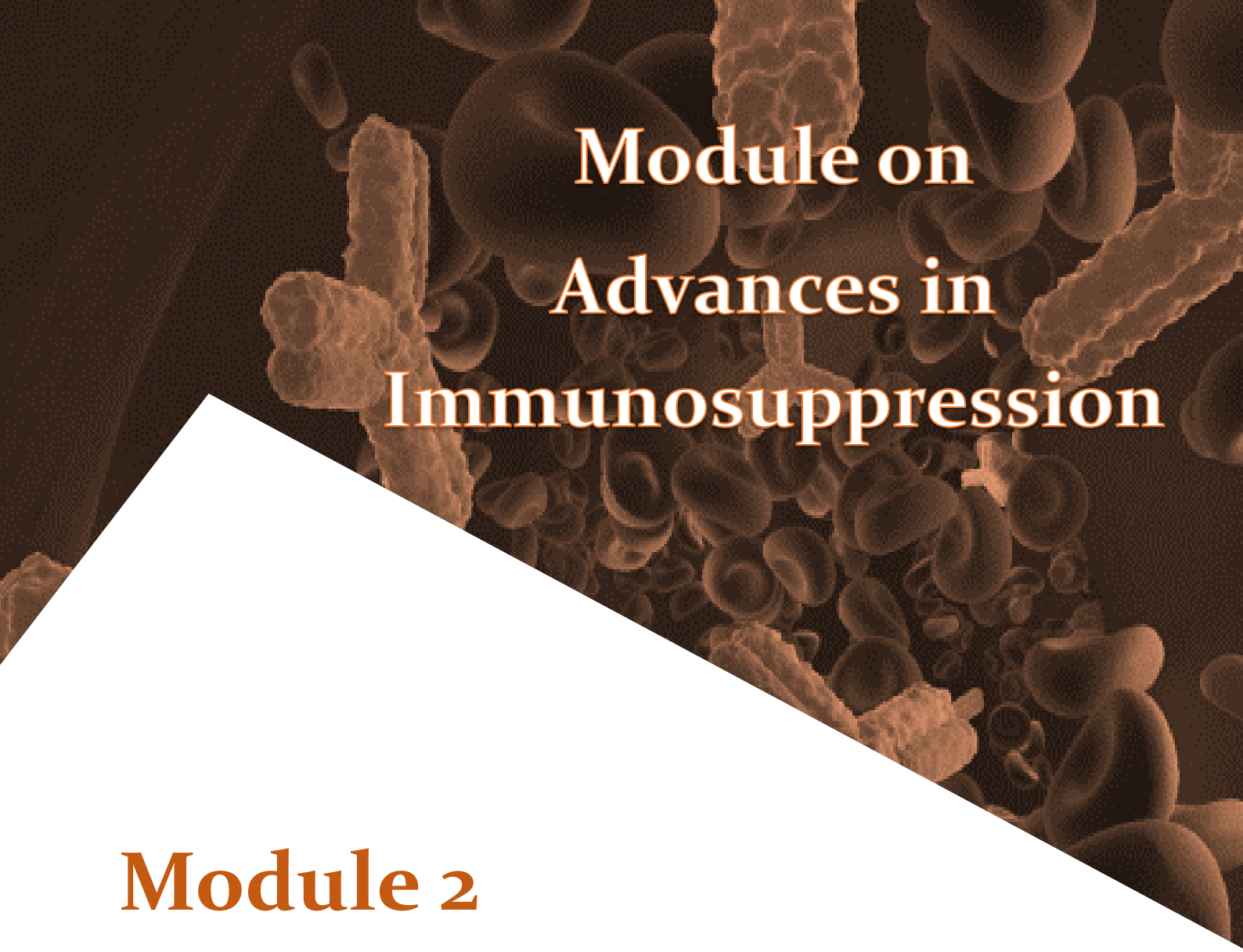

Module on Advances in Immunosuppression

Module 2

Understanding Immunosuppression and Tacrolimus

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Introduction

Tacrolimus (previously known as FK-506) is a macrolide immunosuppressant used for the prevention of allograft rejection in organ transplantation. Approved indications for the drug vary between countries. For example, in the US, tacrolimus is currently approved for use in the prophylaxis of organ rejection (primary therapy) in patients receiving allogeneic liver or kidney transplants. In the UK and Canada, tacrolimus is indicated for both primary therapy and rescue therapy (for graft rejection resistant to conventional immunosuppressive regimens) in liver and kidney transplantation. In Japan, tacrolimus has these indications as well as bone marrow transplantation [(BMT) for primary prevention of graft-versus-host disease (GVHD)]. Several European countries have approved the drug for heart transplantation (rescue therapy or both primary and rescue therapy) as well as liver and kidney transplantation (both primary and rescue therapy). In addition, clinical trials have been conducted with tacrolimus in the prevention and treatment of rejection of lung, pancreas and other allografts.

Although structurally unrelated, tacrolimus and cyclosporin share a similar mechanism of action of immunosuppression Therefore, tacrolimus is used as an alternative to cyclosporin, and tacrolimus-based immunosuppressive regimens have been compared with cyclosporin-based regimens in a number of clinical trials. Although the larger randomised trials conducted to date have been nonblind comparisons of tacrolimus versus the standard formulation of cyclosporin (rather than the more consistently absorbed and widely used microemulsion formulation), several recent studies have compared tacrolimus with cyclosporin microemulsion.

Tacrolimus and cyclosporin are not combined in clinical practice because both drugs have significant nephrotoxic potential. Instead, tacrolimus and cyclosporin are both typically used in combination with a corticosteroid (e.g. prednisone) and an antiproliferative agent (e.g. azathioprine or mycophenolate mofetil), with or without antilymphocyte antibody induction therapy [e.g. muromonab CD3 (OKT3) or antithymocyte globulin]. However, in patients with stable graft function, some concomitant agents may be discontinued.

Molecular and Cellular Immunosuppressive Effects

Tacrolimus acts by a variety of different mechanisms which include inhibition of calcineurin (table I). The drug has a broadly similar cellular mechanism of action to cyclosporin but is 10 to 100 times more potent. Tacrolimus is known to have a wide range of effects in vitro, but the mechanism of action has not yet been entirely defined.

The production of interleukin (IL)-2 and other cytokines by T helper cells is an important event in the immune response and is implicated in graft rejection. Tacrolimus inhibits T lymphocyte activation and transcription of cytokine genes including that for IL-2 (reviewed by Spencer et al., Lang and Baron, Peters et al. and Thomson et al.). The means by which this is achieved are outlined in table I, but the primary event appears to be formation of a complex between tacrolimus and the FK-506 binding protein (FKBP) 12 that binds to calcineurin, inhibiting its phosphatase activity. Transcription of late-phase genes generally is not affected.

As a consequence of its molecular effects, tacrolimus inhibits cell-mediated immune responses. The drug inhibits allogen- and mitogen-induced stimulation of T cell proliferation and inhibits the mixed lymphocyte reaction and generation of cytotoxic T cells. The cytokines produced by T helper (TH)1 cells, which are key to the cell-mediated response, are preferentially suppressed over those produced by TH2 cells, which are important for B cell stimulation and antibody production. Tacrolimus does inhibit humoral immunity, although to a lesser extent than cell-mediated immunity. T cell– dependent B cell activation and proliferation is inhibited, and the drug appears to have a direct effect via inhibition of calcium-dependent B cell activation pathways.

Transforming growth factor (TGF)-β is a multifunctional cytokine with potent immunosuppressive activity and fibrogenic potential, and both tacrolimus and cyclosporin have been shown to induce TGF-β1 hyperexpression in mammalian cells. These results suggest that increased expression of TGF-β1 produced by tacrolimus and cyclosporin may contribute to the immunosuppressive and nephrotoxic properties of these drugs. Previous data had suggested that the increased synthesis of TGF-β induced by cyclosporin in various cells was not shown with tacrolimus.

Graft rejection is dependent on influx of lymphocytes from the circulation into the graft in response to chemotactic factors. As well as inhibiting the production of lymphocyte

chemotactic factors such as IL-8,tacrolimus may have a more generalised inhibitory effect on chemotaxis. It is possible that tacrolimus prevents migration of lymphocytes by inhibiting the protein kinase C-mediated signalling pathway involved in actin polymerisation and cytoskeletal reorganisation.

Tacrolimus does not inhibit the secondary proliferation of activated T cells in response to IL-2, nor does it alter mononuclear phagocyte or natural killer cell function

Hepatic Effects

Tacrolimus appears to have an organ-specific effect in stimulating hepatic regeneration after partial hepatectomy in animals This effect seems to be immunologically based, possibly via modulation of liver cell growth regulatory factors, and is blocked by administration of IL-1α and IL-2. Organ regeneration was not seen with tacrolimus after partial nephrectomy or intestinal resection.

Tacrolimus attenuates hepatic ischaemic or reperfusion injury in animal models. This may be partly attributable to an action of the drug that increases resistance of cells to cytotoxic reactive oxygen species. Tacrolimus, but not cyclosporin, inhibited the induction of inducible nitric oxide synthase (iNOS) expression by inhibiting NF-κB activation in rat hepatocytes. Tacrolimus may prevent hepatic dysfunction by controlling the nitric oxide pathway in addition to its immunosuppressive effect.

Tacrolimus is not thought to cause postoperative cholestasis. A marked reduction occurred in biliary acid secretion (indicating reduced bile acid synthesis) in bile obtained by T-tube drainage in the immediate postoperative period after liver transplantation in patients receiving either tacrolimus or cyclosporin. However, another study that used the duodenal perfusion method showed that the excretory capacity of the liver had completely recovered within 6 to 12 weeks after transplantation in patients receiving tacrolimus, even though serum alkaline phosphatase and γ-glutamyl transferase levels were elevated. This indicates that transplantation-related factors, rather than tacrolimus, cause postoperative cholestasis. In one report, biliary secretion and flow rates recovered more rapidly in tacrolimus than cyclosporin recipients.

Renal Effects

Tacrolimus-induced nephrotoxicity may be functional or structural (reviewed by Trimarchi et al.). Functional toxicity includes hyperkalaemia, hypomagnesaemia, hypertension and renal

dysfunction associated with vasoconstriction and reduced glomerular filtration rate, without significant changes in biopsy specimens. Acute structural nephrotoxicity often manifests as marked tubular changes (e.g. isometric vacuolisation of tubular cell cytoplasm, giant mitochondria and microcalcification), with microvascular changes predominating in some cases. Chronic structural nephrotoxicity often involves chronic tubulointerstitial damage, glomerulosclerosis and hyalin or fibro-mucoid thickening of the arteriolar wall. Tacrolimus-induced renal vasoconstriction is transiently and partially reversible with amino acid infusion that stimulates vasodilation. Although renal vasoconstriction associated with tacrolimus has been demonstrated in animals, data from humans are limited, and preliminary findings of a study of 5 paediatric renal transplant recipients showed no evidence of significant renal vasoconstriction after 4.8 months (mean) of tacrolimus-based immunosuppression.

Metabolic Effects

Immunosuppressive therapy is known to have diabetogenic effects. Post-transplant diabetes mellitus is among the most serious adverse effects of tacrolimus and this may be exacerbated by concomitant administration of corticosteroids. Tacrolimus appears to be more diabetogenic than cyclosporin in some patients.

It has been suggested that tacrolimus has a toxic effect on the endocrine pancreas related to selective localisation of FKBP12 and calcineurin in the islets rather than the acinar tissue, but other mechanisms may also contribute.

As reviewed by Jindal et al. and Spencer et al., preclinical data suggest that tacrolimus suppresses insulin production at the transcriptional level without affecting production of glucagon or insulin receptors. Thus, insulin secretion is reduced and glucose intolerance induced. Morphological damage to islet cells has been reported in animal studies, but is not known to occur in patients treated with tacrolimus. In patients with liver transplants, tacrolimus reduced β cell secretory reserve, and was associated with significant insulin resistance and impaired β cell–α cell axis.

Tacrolimus has been associated with lower serum levels of total cholesterol, triglycerides and/or low density lipoprotein (LDL)-cholesterol than cyclosporin in a number of studies. LDL obtained from renal transplant patients treated with a tacrolimus-based regimen was more susceptible to oxidation than that obtained from either microemulsion cyclosporin-treated patients or normal individuals in an in vitro study. Serum antioxidant levels were significantly lower in the tacrolimus group than in the other groups. These results are in contrast to those

with standard formulation cyclosporin, which has previously been reported to increase the susceptibility of LDL to oxidation. A possible explanation for the lack of adverse effect with the microemulsion cyclosporin formulation is that it contains the antioxidant DLα-tocopherol, although it is unclear whether the amount contained in the formulation is sufficient to play a role in preventing LDL oxidation in the clinical setting. Also, the period of maintenance immunosuppression was markedly shorter among tacrolimus than cyclosporin microemulsion recipients, and the study measured the oxidisability of LDL but not actual amounts of oxidated LDL. Nevertheless, antioxidant supplementation of tacrolimus recipients could prove to be useful. Oxidative modification of LDL and hyperlipidaemia in general contribute to the development of cardiovascular disease and chronic renal graft dysfunction.

Cardiovascular Effects

Transplant-associated coronary artery disease (vasculopathy; TxCAD), which is a major cause of death in cardiac transplant recipients, is thought to be initiated by damage to endothelial cells. The comparative effects of tacrolimus and cyclosporin on factors involved in TxCAD require further clarification. The presence of anti-endothelial antibodies (stimulated by damage to endothelial cells) is thought to correlate with the development of TxCAD. Serial serum samples from 31 cardiac transplant recipients receiving tacrolimus were positive for anti-endothelial (anti-vimentin) antibodies approximately 3 times less often than those from cyclosporin recipients ($p \leq 0.01$) in a 1-year study. On the other hand, pathological microvascular endothelial dysfunction occurred significantly more frequently in patients receiving tacrolimus than those receiving cyclosporin (36 vs 20%; $p < 0.05$) in another 1-year study in 28 cardiac transplant recipients. It has been suggested that such dysfunction is caused by prolonged inflammatory and cytotoxic responses in the allograft related to the transcardiac release of IL-6, greater iNOS gene expression and lesser endothelial cellderived nitric oxide synthase (eNOS) gene expression that occurs with tacrolimus compared with cyclosporin treatment in patients receiving azathioprine and prednisone. Activation of the coagulation system is thought to be involved in TxCAD. Tacrolimus has been reported to have an antithrombotic effect in vitro and ex vivo. This may be mediated by interference of the drug with nuclear translocation of monocyte NF-κB and subsequent reduced transcription of tissue factor.

Immunomodulating Properties of Tacrolimus

T cell activation in response to antigen-specific T cell receptor recognition is associated with integrin-mediated cell adhesion, increased phosphatidylinositol turnover, generation of the intracellular second messengers inositol triphosphate and diacylglycerol (resulting, respectively, in calcium release from the endoplasmic reticulum and activation of protein kinase C), and phosphorylation of cytosolic proteins. Once initiated, these biochemical processes lead to the coordinated expression of gene products, most notably IL-2, crucial for lymphocyte growth and proliferation.

In common with cyclosporin, tacrolimus does not inhibit T cell adhesion, the generation of early second messengers or the increase in intracellular calcium subsequent to T cell receptor recognition; however, the drug does appear to block more distal components of the T cell activation pathway that link these early membrane-associated events and gene expression. Furthermore, tacrolimus appears to be selective for a subset of calcium-associated signal transduction pathways, and these may predominate in the T cell receptor-triggered cascade leading to lymphokine production, thereby accounting for the drug's preferential effect on the immune system.

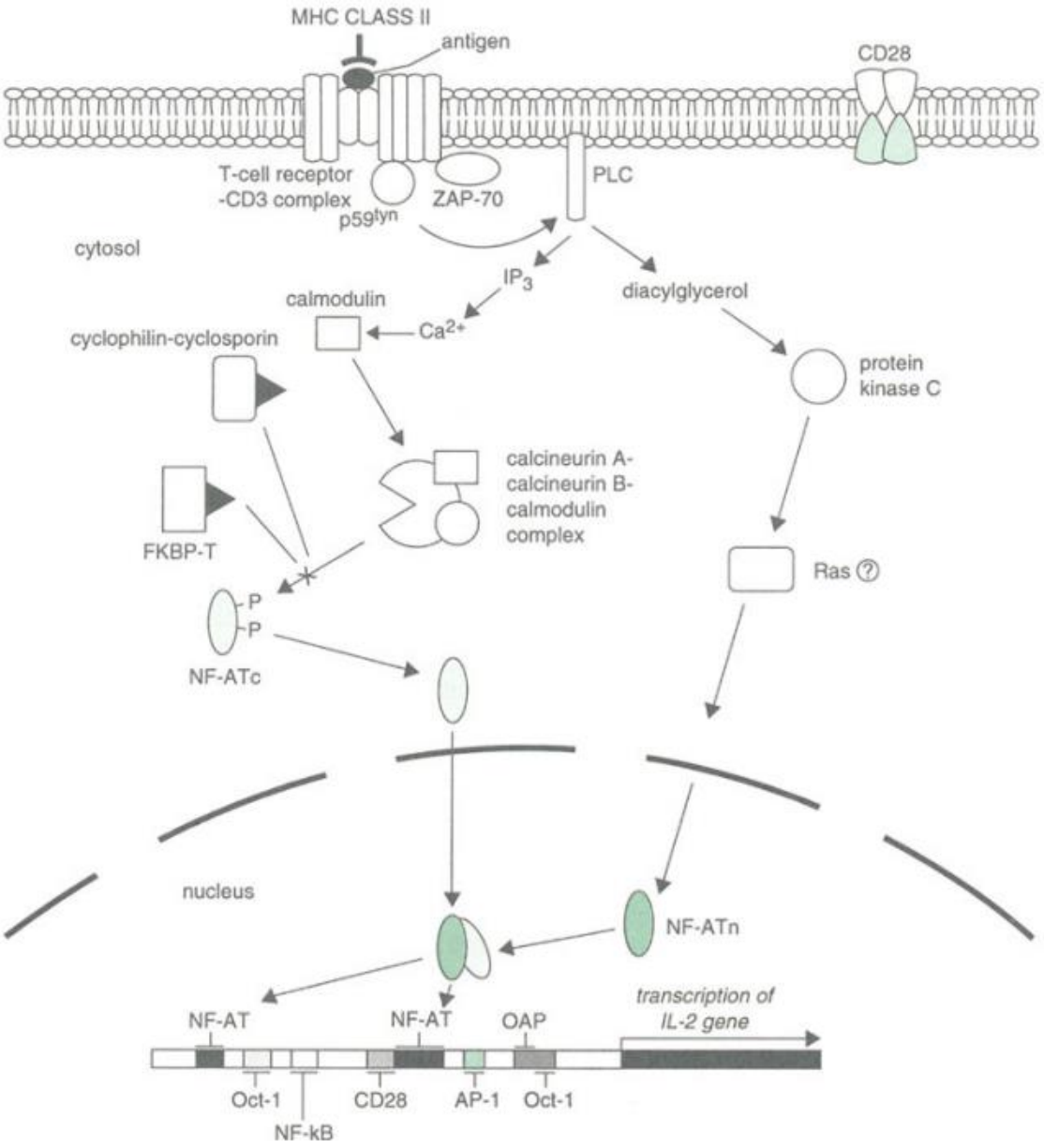

Fig_ 2_ T cell receptor-mediated signal transduction pathways leading to interleukin-2 (lL-2) transcription

Effects on T Cells

In the thymus, developing T cells acquire the antigenic and functional characteristics of mature T cells as they migrate from the cortex to the medulla, before being returned to the circulation_ During this process of thymic maturation, immature thymocytes bearing self-reactive T cell receptors are deleted (clonal elimination). Tacrolimus appears to inhibit thymocyte differentiation and the expression of major histocompatability complex (MHC) class II antigen on thymic epithelial cells. Tacrolimus additionally damages thymic epithelial cells and prevents

programmed cell death (apoptosis) of antigen- and mitogen-stimulated T cell hybridomas, suggesting a potentially deleterious effect on clonal elimination. Thymocyte mobilisation appears to be unaffected by tacrolimus.

Tacrolimus potently inhibits the proliferative response of murine and human T cells to specific antigens, allogeneic lymphocytes and mitogenic lectins in vitro. Both antigen-specific proliferation of cloned helper and cytotoxic T cells and the secondary proliferation of alloreactive T cells generated from mixed lymphocyte reactions (regarded as an in vitro correlate of allograft rejection) and allograft biopsies are sensitive to tacrolimus. Tacrolimus is approximately 100 times more potent than cyclosporin in inhibiting T cell proliferative responses, including mixed lymphocyte reactivity and cytotoxic T cell generation, displaying an 1Cso (concentration required for 50% inhibition of response) of"" 0.1 nmolf. However, tacrolimus has no effect, at micromolar concentrations, on lymphokine (IL-2 and IL-4)-dependent T cell proliferation. The inhibitory effect of tacrolimus on T cell proliferation in vitro is partially reversed by addition of recombinant IL-2 suggesting that, with the exception of IL-2, those gene products and pathways distal to IL-2 remain intact in cells treated with tacrolimus.

The ability of tacrolimus to inhibit lymphocyte proliferation and lymphokine production is governed by the manner of cellular activation. In vitro studies have indicated that tacrolimus inhibits calcium-dependent T cell activation triggered via the T cell receptor-CD 3 complex, the cell surface CD2 receptor, and the combination of protein kinase C activation and calcium influx, but has no effect on calciumindependent T cell activation, such as that triggered via the CD28 surface molecule or protein kinase C activation alone.

Tacrolimus blocks calcium-dependent T cell division between the resting phase (GO) and activation phase (G 1) of the cell cycle, and suppresses the transcription of early phase cytokine genes. Consequently, an antiproliferative effect is only observed when the drug is added within the first few hours of T cell stimulation.

Tacrolimus produces a selective inhibition of cytokine expression by antigen- and mitogen-stimulated T cells, suppressing IL-2, IL-3, IL-4, IL-5, IFN-,)" TNF-a, and GM-CSF production, IL-l-stimulated IFN-')' production, as well as transferrin and IL-2 receptor expression on the T cell surface, while leaving IL-6 (B cell stimulating factor 2) and IL-IO (cytokine synthesis inhibitory factor) production unaffected. These effects are achieved at concentrations (ICso values of"" 0.1 nmolfL) which have no effect on murine bone marrow colony formation in vitro.

Tacrolimus suppresses mixed lymphocyte reactions and the generation of cytotoxic lymphocytes against allogeneic targets, indicating that one of the drug's actions on cellular immune responses is directed against T cells proliferating in response to an alloantigenic stimulus. In vitro cellular cytotoxicity mediated by natural killer (NK) and killer (K) cells and antibody-dependent cell-mediated cytotoxicity is unaffected by tacrolimus. In vivo, tacrolimus is approximately 10 times more potent than cyclosporin in suppressing graft-versus-host reactivity and delayed type hypersensitivity in mice.

Effects on B Cells

The proliferative response of murine and human B cells to anti-Ig antibody, mitogen or ionomycin plus the protein kinase C activator phorbol myristate acetate (PMA) is sensitive to tacrolimus at concentrations which inhibit T cell responses, whereas lipopolysaccharide (LPS)-induced B cell proliferation is unaffected by the drug (Walliser et al. 1989; Wicker et al. 1990). In vitro, tacrolimus inhibits IgM and IgG production by mitogen-stimulated human B lymphocytes, but does not inhibit IL-6 production or IL-6-induced IgM and IgG production. In vivo, tacrolimus suppresses T cell-dependent IgM production by murine and rat splenic plasma cells. Although these effects may be attributed in part to inhibition of lymphokine production by activated T cells tacrolimus also has a direct inhibitory effect on calcium-dependent B cell activation. Thus, tacrolimus blocks induction of TNF-a gene transcription by anti-Ig antibody in human B cells. Tacrolimus additionally appears to inhibit human B cell proliferation in response to certain calcium-independent stimuli, including the protein kinase C activator PMA and IL-2.

In contrast to the situation with the T cell, tacrolimus blocks B cell division in the late activation phase (G 1) of the cell cycle, with the result that substantial inhibition of B cell proliferation is evident when the drug is added as late as 24 hours after stimulation with anti-IgG. Moreover, tacrolimus causes cell death upon activation of murine B cells, whereas in T cells it inhibits apoptosis.

Effects on Nonlymphoid Cells

At concentrations 10- to 100-fold higher than those required to inhibit T cell proliferation, tacrolimus partially suppresses IL-la release from LPS activated human monocytes and alveolar macrophages, and inhibits TNF-a production by antigen- and mitogen-stimulated monocytes.

Through its ability to block T cell lymphokine secretion, tacrolimus might be expected to affect in vivo antigen presentation by inhibiting lymphokine-mediated MHC expression. However, it appears unlikely that direct inhibition of antigen processing contributes significantly to the drug's immunosuppressive action. Moreover, at concentrations which markedly depress T cell proliferation, tacrolimus does not appreciably modify mononuclear phagocyte function.

Tacrolimus has been shown to interfere with a variety of exocytosis-related events in cells of haematopoietic lineage, including IgE receptor-mediated histamine and serotonin release from a rat mast cell line, human skin mast cells and human basophils, and calcium ionophore-induced degranulation of human basophils and neutrophils. The anti-inflammatory activity of tacrolimus is reflected in its inhibition of prostaglandin D2 synthesis in anti-IgE-stimulated human skin mast cells and leuko triene C4 release from human basophils and alveolar mast cells. In vivo, tacrolimus attenuates antigen-induced lung eosinophilia in the guinea pig, platelet activating factor- and leucotriene B4- induced leucocyte adhesion and emigration in postcapillary venules, and ischaemia/reperfusion-induced neutrophil infiltration in the cat small intestinal mucosa. However, calcium-mediated platelet activation and aggregation is unaffected by tacrolimus, indicating that sensitivity to tacrolimus is not a universal characteristic of cells of haemopoietic lineage.

The therapeutic efficacy of tacrolimus as primary immunosuppression and rescue therapy has been evaluated in numerous clinical trials in adult and paediatric patients receiving hepatic, renal or other allografts. Many of the recent studies have been published only as abstracts, but several pivotal trials have been published in full. The following subsections focus on data from prospective randomised studies comparing tacrolimus with cyclosporin-based regimens (standard and microemulsion formulations) as primary immunosuppression. Data from large noncomparative trials, meta-analyses and other contributory studies with tacrolimus as primary therapy are also reviewed, as are studies evaluating tacrolimus as rescue therapy. It is important to highlight some issues relating to study design in the comparisons between tacrolimus- and cyclosporin-based immunosuppressive regimens.

Hepatic Transplantation

Several randomised prospective studies have compared tacrolimus- with cyclosporin-based immunosuppressive regimens as primary therapy in hepatic transplantation. Table III includes 2 large multicentre studies, one conducted in the USand the other in Europe, which used the standard formulation of cyclosporin. Smaller singlecentre trials comparing tacrolimus with the standard formulation of cyclosporinhave not been included in the table, as results were generally similar to those of the multicentre trials. Table III also includes a number of small randomised comparative trials that used the cyclosporin microemulsion formulation, since it has generally replaced the standard formulation of cyclosporin in recent years.

In the larger studies comparing tacrolimusbased regimens with those including the standard formulation of cyclosporin, patient and graft survival rates were similar between treatment groups at 1 year post-transplantation, although rates were numerically higher with tacrolimus-based immunosuppression (table III). The proportion of tacrolimus recipients alive at 1 year was 83% in the European trial and 88% in the US study; graft survival was 78 and 82%, respectively. Corresponding results among cyclosporin recipients were 78 and 88% for patient survival, and 73 and 79% for graft survival. Likewise, follow-up data at 3 years in the European study and at 5 years in the US studyshowed a similar tendency as observed at 1 year post-transplantation (table III). Pooled data from a sample of 1000 patients who entered the 2

multicentre studies showed a statistically significant advantage for tacrolimus in terms of both patient and graft survival at 3 years post-transplantation.

Long term estimates of patient and graft 'halflife survival', calculated using data from patients who survived with an intact graft at 1 year in the large multicentre US trial, are presented in figure 1. Although not clearly defined by the study authors, it appears that patient and graft 'half-life survival' values for these patients reflect projected estimates of the time at which 50% of patients or grafts will have survived (and 50% will not have survived). Patient half-life survival was significantly longer with tacrolimus- than with cyclosporin-based therapy in this subgroup of patients (25.1 vs 15.2 years; $p < 0.05$), but graft half-life survival did not differ significantly.

Fewer patients receiving tacrolimus than cyclosporin were converted to the alternative drug because of rejection in the US multicentre study (this was necessary in 3 tacrolimus vs 22 cyclosporin recipients) and in a smaller single-centre comparative trial (1 vs 40 patients). The US multicentre trial and 3-year follow-up data from the European multicentre study showed a significant corticosteroid-sparing effect of tacrolimus relative to cyclosporin in terms of cumulative corticosteroid dosage per patient. In addition, 3-year data from the European trial demonstrated a significantly greater proportion of patients had been withdrawn from corticosteroids in the tacrolimus group (80 vs 68%; $p < 0.05$).

Renal Transplantation

A number of randomised prospective nonblind studies have compared tacrolimus- and cyclosporin-based immunosuppressive regimens as primary therapy in renal transplantation. Table IV includes 2 large multicentre studies, one conducted in the US and the other in Europe, which compared tacrolimus with the standard formulation of cyclosporin. Smaller randomised trials as well as nonrandomised or retrospective analyses comparing tacrolimus with the standard formulation of cyclosporin have not been included in the table, as results were generally similar to those of the randomised multicentre trials. Also included in table IV are prospective randomised trials which compared tacrolimus with the microemulsion formulation of cyclosporin, since it has generally replaced the standard formulation of cyclosporin in contemporary practice. Both of the large multicentre randomised studies in renal transplant patients demonstrated high rates of patient (≈95%) and graft (≈85 to 90%) survival at 1 year post-transplantation with tacrolimus-based regimens or those including the standard

formulation of cyclosporin, and there were no statistically significant differences between groups for these parameters (table IV).

Both studies also showed a statistically significant advantage favouring tacrolimus for (biopsyconfirmed) acute rejection rates (26 vs 46% or 31 vs 46%; both $p < 0.001$). Four-year data from the European study showed similar patient and graft survival rates between treatment groups (table IV) and a nonsignificant trend towards a lower rate of chronic rejection among tacrolimus than cyclosporin recipients (5.5 vs 11.3%). Three-year survival data have been reported for the US cohort, and these were similar between treatment groups (≈90% for patient survival and ≈80% for graft survival; table IV). However, tacrolimus was associated with significantly fewer graft failures (excludes death as a reason for graft loss) than cyclosporin over the 3-year period (10.2 vs 16.4%; $p < 0.05$). In addition, fewer patients receiving tacrolimus than cyclosporin were converted to the alternative drug (for any reason) in the US study; this was necessary in 8.3% of tacrolimus and 24.2% of cyclosporin recipients during the 3-year study ($p < 0.05$). The majority of patients who were converted from cyclosporin to tacrolimus had refractory rejection (usually during the first year), and in most cases the renal allografts were successfully rescued. When crossover due to rejection was considered a graft loss, graft survival rates at 3 years post-transplantation were significantly higher among tacrolimus than cyclosporin recipients (81.5 vs 70.0%; $p < 0.005$).

Heart Transplantation

Most studies of tacrolimus-based regimens as primary therapy in adult heart transplant recipients have been comparisons with cyclosporin-based regimens (standard formulation or formulation not specified), and results of these trials are presented in table V. An additional randomised trial of 85 patients has been excluded from the table because results were not presented in a format suitable for inclusion.

In the studies included in table V, patient survival rates at 1 and ≈2 years post-transplantation ranged from 80 to 90% with tacrolimus-based regimens compared with similar rates of 81 to 93% with cyclosporin-based regimens. Five-year survival rates were also similar between tacrolimus and cyclosporin treatment groups (76 vs 71%) in the trial with the longest follow-up period and greatest number of patients ($n = 243$). Although this study was conducted prospectively, it was nonrandomised and included both adult and paediatric patients. Approximately 34% of patients receiving tacrolimus were $p < 0.01$).

Other Solid Organ Transplantation

Lung Transplantation in Adults

The efficacy of tacrolimus as primary immunosuppressive therapy in patients with lung transplantation has been evaluated in 2 comparative trials with cyclosporin, one of which was a prospective randomised analysis of 133 patients, the other a smaller retrospective study. In the prospective randomised trial no significant differences were noted between tacrolimus and cyclosporin treatment groups in 1- (83 vs 71%) and 2-year (76 vs 66%) patient survival rates, and at the latest follow-up, mean survival time for patients receiving tacrolimus was 1115 days (3.05 years) compared with 1012 days (2.77 years) for those receiving cyclosporin. Although there was a trend towards a greater proportion of tacrolimus than cyclosporin recipients who were free from acute rejection (14 vs 11.5%), the difference between treatment groups was not statistically significant. Tacrolimus recipients had a significantly lower incidence of obliterative bronchiolitis (21.7 vs 38%; $p < 0.05$), which is the histological manifestation of chronic rejection and is the leading cause of morbidity and mortality in patients with lung transplants. Also, fewer tacrolimus than cyclosporin recipients required crossover to the alternative immunosuppressant because of rejection or for other reasons (5 vs 15; $p < 0.05$).

Pancreas or Kidney and Pancreas Transplantation in Adults

Any discussion of immunosuppression after pancreas transplantation must take into account that graft survival after simultaneous pancreas and kidney transplantation (SPK) is greater, and the incidence of acute rejection episodes is lower, than that after pancreas transplant alone (PTA) or pancreas after kidney transplant (PAK). Tacrolimus is usually used in combination with corticosteroids and either mycophenolate mofetil or azathioprine as primary immunosuppressive therapy. Antilymphocyte antibody induction therapy is commonly used in this setting, especially in PTA recipients where its use is almost mandatory because of the high risk of rejection and subsequent graft loss. Nevertheless, the need for antibody induction therapy in pancreas transplantation remains somewhat controversial, primarily because of a low rate of acute rejection among a large cohort of pancreas transplant recipients (n = 123; 85% SPK) treated without antibody induction therapy at the University of Pittsburgh. Guidelines for tacrolimus dosage regimens, target tacrolimus trough blood levels and other aspects of primary immunosuppression in pancreas transplant recipients have been provided recently by Gruessner et al.

Longer term data from another single-centre trial of 60 patients (55 of whom underwent SPK transplantation) receiving tacrolimus-based immunosuppression showed 2- and 3-year patient survival rates of 98 and 97%. Pancreatic graft survival rate was 80% at 2 years and unchanged at 3 years post-transplantation, and corresponding renal graft survival rates were 93 and 91%. Corticosteroid withdrawal was achieved in 65% of patients with a functioning pancreas (31 of 48 patients). Additional studies primarily focusing on SPK recipients have also shown that corticosteroids can be successfully discontinued in patients receiving tacrolimus-based immunosuppression. Statistically significant differences favouring tacrolimus recipients, when compared with historical controls given cyclosporin, were noted in the number of or time to acute rejection episodes after SPK in some trials, including 1 study in which approximately half of the patients in the tacrolimus group (9 of 16) received induction therapy with daclizumab or basiliximab.

Cyclosporin-treated patients with pancreas transplantation who have persistent acute rejection generally respond well to tacrolimus rescue therapy, with marked reductions in acute rejection episodes and good patient and graft survival rates. Some analyses focused on or also included patients who were converted to tacrolimus because of significant drug-related adverse events associated with cyclosporin. Most reports have included only small numbers of patients ($n < 15$) converted from cyclosporin to tacrolimus, but 2 studies were much larger.

Intestinal Transplantation

Several reports involving small numbers of patients indicate that tacrolimus is effective in this clinical setting. Data from the International Transplant Registry ($n = 170$) indicate that, depending on the subgroup of intestinal transplant recipients, tacrolimus-based primary immunosuppression is associated with 1- and 3-year patient survival rates of 59 to 83% and 40 to 47%, respectively, and 1- and 3-year graft survival rates of 51 to 65% and 29 to 38%, respectively. In general, patient and graft survival rates were as good as or better than those achieved with cyclosporin-based regimens. Among cyclosporin recipients, 1- and 3-year patient survival rates were 41 to 57% and 28 to 50%, respectively, and 1- and 3-year graft survival rates were 17 to 44% and 11 to 41%, respectively

Bone Marrow Transplantation

For several years the established therapy for prevention of GVHD in patients receiving allogeneic BMT has been cyclosporin plus methotrexate, with or without corticosteroids.

However, as experience with tacrolimus has been gained in a number of small- and moderate-sized noncomparative or nonrandomised trials, it has become evident that tacrolimus may also be a useful agent for the prevention of GVHD following BMT. Results of the 3 randomised comparative trials consistently demonstrated a significantly lower incidence of grade II to IV acute GVHD with tacrolimus- than cyclosporin-based therapy.

Tacrolimus has also been used in the treatment of patients who developed acute or chronic GVHD while receiving cyclosporin-based immunosuppressive therapy after BMT. One study also evaluated patients who developed significant drugrelated toxicity with cyclosporin and were converted to tacrolimus.

Tolerability

The principal adverse effects associated with tacrolimus treatment include nephrotoxicity, neurotoxicity, disturbances in glucose metabolism, gastrointestinal (GI) disturbance and hypertension. Susceptibility to infection and malignancy is also increased. All of these adverse effects also occur with cyclosporin, although the incidence of some adverse effects differs between the drugs. Tacrolimus is rarely associated with the cyclosporin-specific adverse effects hirsutism, gingivitis and gum hyperplasia, but it may cause alopecia and pruritus in some patients.

Many of the adverse effects of tacrolimus are dose-related; nephrotoxicity, neurotoxicity, glucose metabolism disturbances, GI disturbances and infections may occur more frequently or be more severe at higher whole-blood tacrolimus concentrations. Importantly, these adverse events can often be managed by dosage reductions. Concomitant drugs such as corticosteroids may also contribute to some adverse effects.

In the major trials in patients undergoing liver or kidney transplants, withdrawal rates because of adverse events tended to be higher with tacrolimus than cyclosporin. Nephrotoxicity occurred in as many as half of patients treated with either tacrolimus or cyclosporin. Neurotoxicity associated with tacrolimus most frequently manifests as tremor, headache, insomnia and paraesthesia, and some neurological effects (including tremor and paraesthesia) may be more problematic with tacrolimus than with cyclosporin.

Diabetes mellitus and/or hyperglycaemia also tended to occur more frequently with tacrolimus than with cyclosporin in the major trials in kidney or liver transplant recipients. In 2 large multicentre randomised kidney transplantation trials, the incidence of new-onset type 1 diabetes mellitus was 20 vs 4% in the US trial and 8 vs 2% in the European study. However, about one-quarter to one-third of affected tacrolimus recipients were able to discontinue insulin therapy within 1 year. Furthermore, tacrolimus has generally not been more diabetogenic than cyclosporin in cardiac transplant trials. Also, at least 1 recent study in renal transplant recipients showed a lower incidence of post-transplantation diabetes mellitus with tacrolimus than in previous reports, suggesting that, with more experience, it may be possible to reduce the risk of developing this complication. Other metabolic disturbances that can occur with tacrolimus include hyperkalaemia and hypomagnesaemia.

A number of studies have shown that tacrolimus has less adverse effect than cyclosporin on lipid profiles and/or the general cardiovascular risk profile. In particular, significantly lower serum levels of total cholesterol, triglycerides and/or low density lipoprotein-cholesterol have been reported with tacrolimus. Hypertension occurred in up to half of patients treated with tacrolimus in major trials, but it was normally mild to moderate in severity, whereas hypertension can be more severe with cyclosporin. In cardiac transplant recipients, hypertension requiring treatment occurred more frequently with cyclosporin- than tacrolimusbased regimens.

GI disturbance, including diarrhoea, nausea and constipation, occurs commonly in patients treated with tacrolimus; diarrhoea is more frequent with tacrolimus than with cyclosporin.

Infection rates were similar in tacrolimus- and cyclosporin-treated groups in the major clinical trials in kidney or liver transplant recipients.

The tolerability profile of tacrolimus in children is generally similar to that in adults. However, children are at increased risk of potentially fatal Epstein-Barr virus–related post-transplant lymphoproliferative disorders (PTLD). The incidence of PTLD in paediatric liver transplant recipients may be higher with tacrolimus- than cyclosporin-based immunosuppression. From the reported experiences (in >10 patients) of using tacrolimus in primary liver transplantation in children, the incidence of PTLD usually ranged from 3 to 11%, although higher values have been reported. The incidence of PTLD in paediatric patients converted to tacrolimus therapy appears to be higher than that in primary therapy, but this may be associated with high cumulative dosages of immunosuppressive agents required to treat intractable rejection.

The risks of tacrolimus treatment during pregnancy appear to be no greater than those with cyclosporin, and it has been suggested that tacrolimus may be associated with a lower incidence of maternal hypertension or pre-eclampsia.

Whenever possible, tacrolimus should be initiated using the oral route of administration. For patients unable to take tacrolimus orally, therapy may be initiated by continuous intravenous infusion. In the US, the recommended intravenous starting dose is 0.03 to 0.05 mg/kg/day for adults receiving liver or kidney transplantation and for children receiving liver transplantation; no specific recommendation for paediatric kidney transplantation is provided in US prescribing information. In the UK, initial intravenous dose recommendations for adults are 0.01 to 0.05 mg/kg/day for liver and 0.05 to 0.10 mg/kg/day for kidney transplantation; corresponding recommendations for children are 0.05 mg/kg/day for liver and 0.1 mg/kg/day for kidney transplantation. Conversion from intravenous to oral therapy should occur as soon as is clinically feasible, usually within 2 to 3 days. Whether administered by the oral or intravenous route, the initial dose of tacrolimus should begin approximately 6 hours after the completion of liver transplant surgery and within 24 hours of kidney transplantation surgery.

Oral tacrolimus is administered in 2 divided daily doses at 12-hour intervals. In adults, the recommended starting oral dosage of tacrolimus as primary immunosuppression is 0.10 to 0.15 mg/kg/day (US) or 0.10 to 0.20 mg/kg/day (UK) for liver transplantation and 0.2 mg/kg/day (US) or 0.15 to 0.30 mg/kg/day (UK) for kidney transplantation. Initial recommended dosage in children receiving liver transplantation is 0.15 to 0.20 mg/kg/day (US) or 0.3 mg/kg/day (UK). In the UK, 0.3 mg/kg/day is the recommended initial dose of tacrolimus in paediatric renal transplant recipients; US prescribing information does not provide a corresponding recommendation for this patient population.

During maintenance therapy the dose of tacrolimus can often be reduced. In general, children require higher doses than adults to achieve similar blood concentrations of tacrolimus. Likewise, African-American patients typically require higher tacrolimus doses than Caucasian patients (at least in kidney transplantation) to achieve similar blood concentrations of the drug. Patients with hepatic or renal dysfunction should receive doses at the lowest value of the recommended intravenous and oral dosage ranges (and further dosage reductions may be required).

When tacrolimus is used as rescue therapy in patients not responding to (or not tolerating) cyclosporin-based therapy, treatment should begin with the same initial dosage as for primary

therapy in that particular allograft (UK recommendation). Tacrolimus should not be started until approximately 24 hours after discontinuation of cyclosporin therapy.

References:

1. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. Drugs. 2000;59(2):323-389.
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