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CHAPTER 10.8

TACROLIMUS AND THERAPY OF HUMAN AUTOIMMUNE DISORDERS

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INTRODUCTION

Tacrolimus (formerly known as FK506) is a macrolide antibiotic isolated from the soil fungus *Streptomyces tsukubaensis*.[1] Although it is totally distinct in molecular structure from cyclosporine A (CsA), a cyclic endecapeptide extracted from the fungus *Tolypocladium inflatum*, the two immunosuppressants share a remarkably similar, selective inhibitory action on the activation and proliferation of $CD4^+$ T helper (TH) lymphocytes[2-6] (see also chapter 10.3). In 1989, the first account of the ability of tacrolimus to prevent or reverse human organ allograft rejection was published.[7] Data obtained over the ensuing 5 years have provided good evidence that tacrolimus is at least as valuable an investigational tool and clinical immunosuppressive agent as CsA.[8,9] Multicenter, prospective, randomized controlled trials of tacrolimus versus CsA in primary liver transplantation have shown significantly reduced rates of acute rejection and reduced steroid requirements in the tacrolimus arm of the trials. In April 1994, tacrolimus was approved by the US Food and Drug Administration for the therapy of liver allograft rejection. Whilst the potential benefits of tacrolimus in organ transplantation are now widely recognized, the prospective value of the drug in the treatment of autoimmune disorders is now also being assessed. In this chapter, we discuss the rationale for the use of tacrolimus in autoimmune disease, and report on the early clinical experience with the drug in the management of a variety of autoimmune diseases conducted principally at the University of Pittsburgh Medical Center (UPMC) (Table 10.8.1).

RATIONALE FOR THE USE OF TACROLIMUS IN AUTOIMMUNE DISEASES

The therapeutic use of tacrolimus in a particular autoimmune disease is based on the premise that the disorder is T cell driven.[10] In autoimmune uveitis,[11] type I diabetes,[12] multiple sclerosis,[13] psoriasis,[14] and rheumatoid arthritis for example, T cells are believed to play an important pathogenic role. Much of

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the evidence to support this view comes from studies in experimental animals and from investigations in vitro of the adverse or destructive interactions between T cells, antigen-stimulated T cell-derived cytokines and the target tissue affected by the disease process. In the autoimmune liver diseases,[15] chronic active hepatitis (CAH), primary biliary cirrhosis (PBC) and in rheumatoid arthritis,[16] there is abundant evidence for the involvement of T cells in the pathogenesis of each disease and therefore a rationale for the use of tacrolimus in each exists. In recent years, the therapeutic efficacy of CsA in sight-threatening uveitis, severe psoriasis, PBC, CAH and rheumatoid arthritis has been demonstrated.[17] Moreover, CsA has been shown to alter the natural history of recent onset type-I diabetes.[18] Notably however, CsA has not made a significant impact upon the clinical management of patients with most of these diseases.

In autoimmune diseases such as systemic lupus erythematosus (SLE), or the nephrotic syndrome, the rationale for the use of CsA or tacrolimus is less clear. Thus in SLE, humoral immunity appears to be more important than cellular immunity in the pathogenesis of the disease, while in idiopathic nephrotic syndrome, the pathogenic mechanisms are far from clear. Nevertheless, T cell dysfunction, recruitment of B-lymphocytes and immunoglobulin deposition within the kidney and a central role for lymphokines in nephrotic syndrome have been implicated by various authors.[19-22] In addition, CsA has been shown to be very effective in steroid-sensitive nephrotic syndrome, although less so in steroid-resistant patients.[17]

The predicted efficacy of tacrolimus in a particular human autoimmune disorder is based on the assumption that the role of T cells is central to the disease process. It is also based on experience in animal models of these diseases treated with either CsA or tacrolimus (see chapter 10.3). Account is also taken of previous clinical experience with CsA in these diseases.

COMPARATIVE BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF TACROLIMUS AND CsA

Although distinct in molecular structure, tacrolimus and CsA share many biological and pharmacological properties (e.g., binding to intracellular immunophilins, selective interference with $CD4^+$ T cell function, rate of systemic absorption, plasma half-lives, etc.). These similar properties of the two immunosuppressants are

Table 10.8.1. Protocols for treatment of autoimmune diseases utilizing tacrolimus at the University of Pittsburgh Medical Center

Eye and ear diseases
Uveitis; scleritis
Ocular cicatrical pemphigoid
Autoimmune inner ear disease
Neurologic
Multiple sclerosis; amyotrophic lateral sclerosis
Renal
Nephrotic syndrome
Gastrointestinal
Ulcerative colitis
Crohn's disease
Chronic active hepatitis (autoimmune)
Primary sclerosing cholangitis
Primary biliary cirrhosis
Celiac sprue
Skin
Psoriasis
Pyoderma gangrenosum
Epidermolysis bullosum
Alopecia universalis
Endocrine
New onset type I diabetes
Collagen vascular disease/vasculitis
Behcet's disease
Scleroderma
Rheumatoid arthritis
Polymyositis/dermatomyositis
Wegener's granulomatosis

Table 10.8.2. Biological and pharmacological properties of tacrolimus and CsA

Similarities
- Molecular action and antilymphocytic activity (similar actions on $CD4^+$ T cells and cytokine generation)
- Interfere with T cell maturation (reversible)
- Immunosuppressive and toxic effects related mechanistically
- Inhibition of mast cell degranulation
- Bind to intracellular immunophilin (CsA to cyclophilin; tacrolimus to FKBP)
- Inhibition of apoptosis
- Absorbed orally
- Metabolized in liver (cyt P450 mixed function oxidases)
- Metabolites are excreted into bile
- Wide tissue distribution (lipophilic)
- Plasma 1/2 lives (CsA 5-12hr; tacrolimus 4-14hr)
- Absorption (CsA 2-4 hr; tacrolimus 1/2-4hr)
- Not excreted in urine (< 2%)
- Metabolites ineffective
- Oral absorption (CsA 30%; tacrolimus 35%)
- Drug interactions (e.g. erythromycin; ketoconazole)
- Hepatotrophic
- Predominant blood distribution in RBC

listed in Table 10.8.2. Properties of tacrolimus and CsA which are known to differ are shown in Table 10.8.3. Of special significance, in relation to the potential value of the drugs in autoimmune diseases, is the superior capacity of tacrolimus, compared with CsA, to reverse cell-mediated immunity (e.g., allograft rejection or graft-versus-host disease).

INFLUENCE OF TACROLIMUS ON EXPERIMENTAL AUTOIMMUNE DISEASES

Tacrolimus is effective in inhibiting a wide variety of experimental autoimmune disorders in rodents and in larger laboratory animals (see previous chapter). The autoimmune diseases in which the immunosuppressive efficacy of tacrolimus has been proven include uveitis, type-I diabetes, thyroiditis, autoimmune renal disorders, experimental allergic encephalomyelitis (a correlate of multiple sclerosis) and autoimmune myocarditis. An example of the inhibitory effect of tacrolimus on experimental autoimmune disease is shown in Figure 10.8.1. PVG/c female rats which have been neonatally thymectomized and sublethally irradiated subsequently develop autoimmune thyroiditis. The development of the disease is inhibited by a 3-week course of systemic tacrolimus starting after demonstration of serological evidence of autoantibody (anti-thyroglobulin antibody) production.[23] Some untreated disease control animals also develop insulitis. This is also prevented by tacrolimus administration.

Table 10.8.3. Biological and pharmacological properties of tacrolimus and CsA

Differences
- Molecular structure
- Immunophilins distinct
- Therapeutic level (CsA μg ml; Tacrolimus: ng/ml)
- CsA absorption (but not that of Tacrolimus) dependent on bile flow
- Tacrolimus (but not CsA) reverses cell mediated immunity (GVHD, allograft rejection)
- Drug interactions—no change of Tacrolimus level with the combination of calcium channel blockers
- Hypogonadism (male especially & female)(CsA)
- Antilymphocytic effects of Tacrolimus less easily reversed (in vitro)

EARLY CLINICAL EXPERIENCE WITH TACROLIMUS AT THE UNIVERSITY OF PITTSBURGH MEDICAL CENTER

Primary Sclerosing Cholangitis (PSC)

A total of 11 cases of primary sclerosing cholangitis (PSC) have been treated with tacrolimus in the autoimmune clinic at UPMC. Most of these cases have also had ulcerative colitis. A few have either had Crohn's colitis (n = 4) or no colonic disease at all (n = 4). The biochemical responses of a representative responder with PSC and ulcerative colitis to tacrolimus therapy is shown in Figure 10.8.2. A dramatic decline in total bilirubin and alkaline phosphatase occurred early, with a later reduction in the ALT and AST levels.

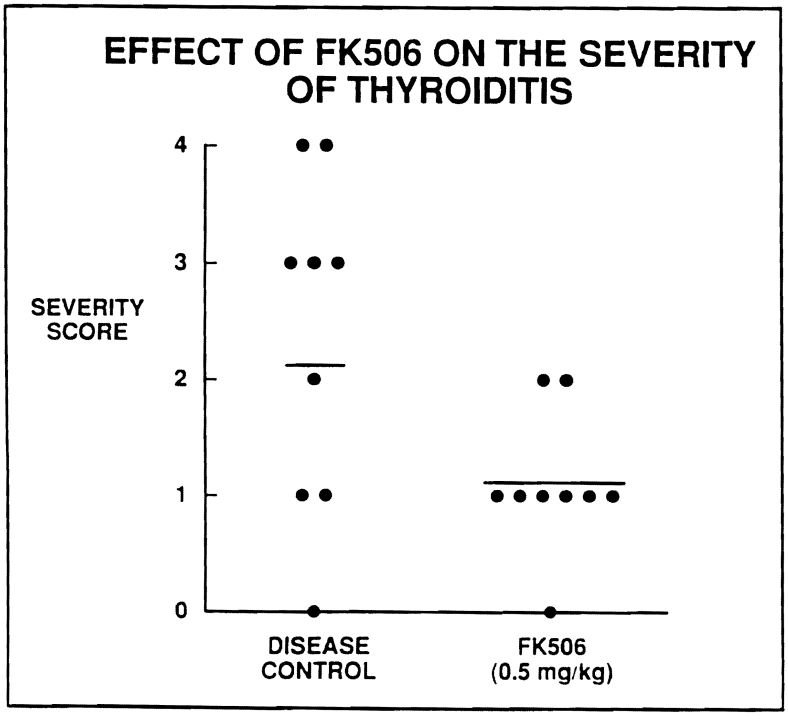

Fig. 10.8.1. Inhibitory effect of tacrolimus (FK506) on experimental autoimmune thyroiditis. For further details see Tamura et al.[23]

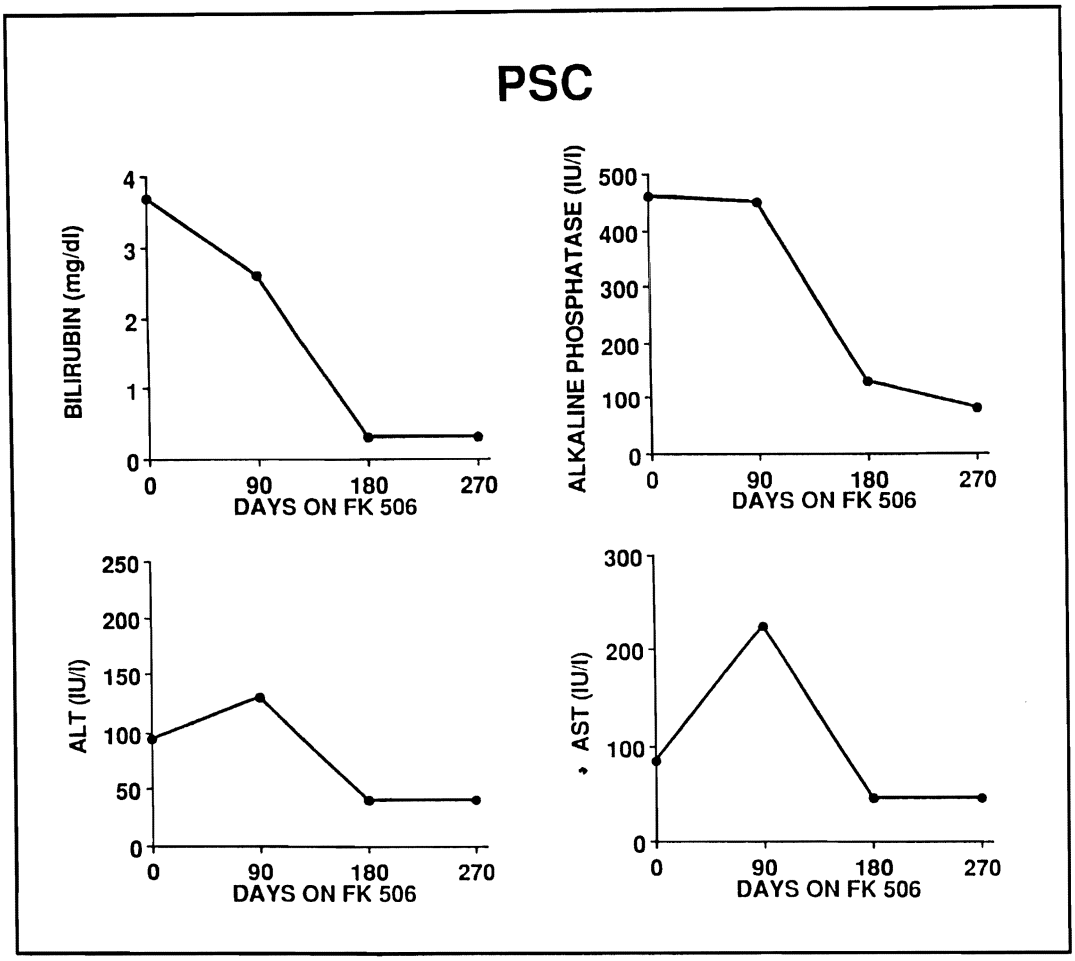

Fig. 10.8.2. Biochemical responses (serum total bilirubin, alkaline phosphatase, ALT and AST levels) in a representative responder with PSC treated with tacrolimus (FK506). Reproduced from Jhanson AW et al. Springer Semin Immunopathol 1993; 14: 323-344.

Primary Biliary Cirrhosis (PBC)

Sixteen patients with PBC have been treated with tacrolimus in the autoimmune clinic of UPMC. The majority of these cases have been women. Most but not all have shown a response to tacrolimus therapy, as illustrated in Figure 10.8.3, with a marked reduction in the serum bilirubin and alkaline phosphatase levels and with modest reductions into the normal range for serum ALT and AST levels.

Autoimmune Chronic Active Hepatitis (CAH-A)

Twenty one cases of autoimmune CAH have been treated with tacrolimus at UPMC. The majority have been women. Half had failed to respond to glucocorticoids alone or used in combination with azathioprine. One failed with CsA. Elevated bilirubin and transaminase levels declined into the normal range with the institution of tacrolimus (Fig. 10.8.4). Of the three hepatic diseases that have been treated with tacrolimus, this group with autoimmune CAH appears to respond best and most consistently.

Crohn's Disease

A total of 17 patients with Crohn's disease have been treated with tacrolimus at UPMC. Most have had complicated diseases, involving the colon or colon and small bowel with multiple perianal, vaginal, vesicular or cutaneous fistulae. Tacrolimus treatment has, in all cases, been followed by a reduction in the amount of drainage and in most cases, by drying up of fistulous tracts. Enteric disease has not been eradicated with tacrolimus, however its use has allowed complications of Crohn's disease to resolve such that surgical repair has become possible in some cases. A beneficial use of tacrolimus in this disease process may therefore be in the preoperative management of cases. In individual subjects, an apparently inoperable case could be converted to an easily resectable one with the use of tacrolimus. Moreover, its use preoperatively may enable the patient to go to surgery without the use of steroids that complicate healing and foster infection in the early postoperative period.

Ulcerative Colitis

Nineteen cases of ulcerative colitis have been treated with tacrolimus. Eleven patients also have PSC, while 6 do not have confounding PSC. A clear response of the symptoms or the underlying pathology to tacrolimus treatment has not been noted; however treatment has enabled several of the patients without PSC to stabilize their disease activity and

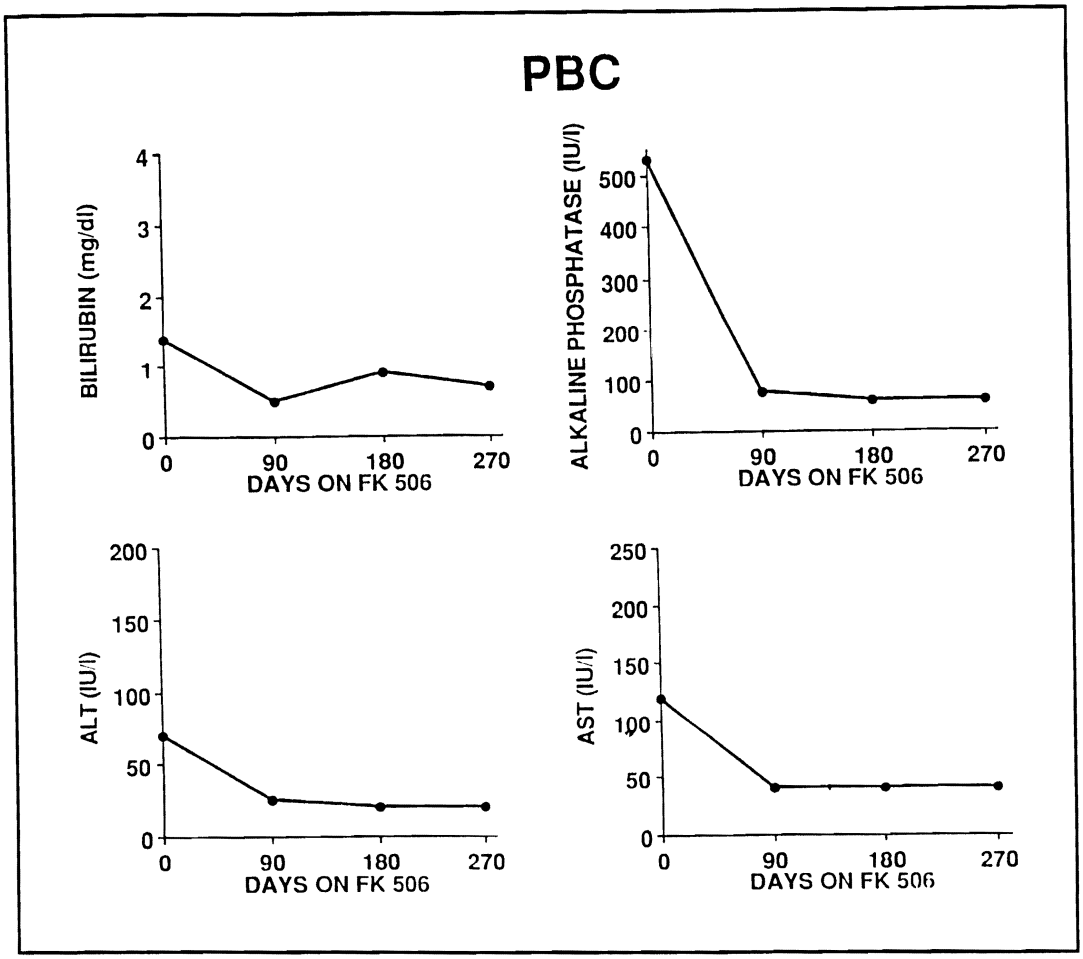

Fig. 10.8.3. Biochemical responses (serum total bilirubin, alkaline phosphatase, ALT and AST levels) in a representative responder with PBC treated with tacrolimus (FK506). Reproduced from Jhanson AW et al. Springer Semin Immunopathol 1993; 14: 323-344.

undergo surgery to treat a complication of the disease, usually a colonic stricture. The role of tacrolimus in the management of ulcerative colitis appears to be less clear than in the treatment of Crohn's disease and its complications.

Sprue (Celiac Disease)

Four patients with sprue documented by (1) the presence of gluten sensitivity (2) an atrophic small bowel mucosa on intestinal biopsy and (3) the presence of detectable reticulum antibodies have been treated with tacrolimus. One of these 4 cases had failed gluten withdrawal and had required total parenteral nutrition (TPN) for several years prior to the use of tacrolimus. Three patients are able to eat a normal diet containing gluten without the development of symptoms while taking tacrolimus. D-xylose absorption has improved in all 4 subjects, but remains abnormal in the single patient who had required TPN for several years prior to the institution of tacrolimus. On tacrolimus, the appearance of intestinal biopsies improved in all cases. The improvement has been rather small however, in the single case that had required TPN to maintain her nutritional status prior to the use of tacrolimus. Neurotoxicity limited increasing the dose of tacrolimus in this patient whose levels remained in the low therapeutic range during treatment. Nonetheless, the extraintestinal consequences of her disease, hypogonadism, cheilitis, hair loss, fatigue and seizures related to hypocalcemia resolved or improved while on tacrolimus.

Uveitis/Scleritis (n = 3)

Tacrolimus appears to be of benefit in these conditions.[24] One patient with scleritis who was refractory to CsA has responded to tacrolimus. Preliminary data appear to show that steroid use will still be required in these conditions, although at a reduced dose. Mochizuki and his colleagues (Kurume University School of Medicine, Fukuoka, Japan) have reported on the efficacy of tacrolimus in refractory uveitis in 8 patients, 5 with Behcet's disease and 3 with idiopathic retinal vasculitis.[25] The mean observation period was 22 weeks. Seven of the cases had no side effects; 1 patient developed moderate renal impairment. The effects of tacrolimus by the criteria of improved visual acuity and uveitis activity were dose dependent. In most cases, 0.15 and 0.2 mg/kg/day were effective.

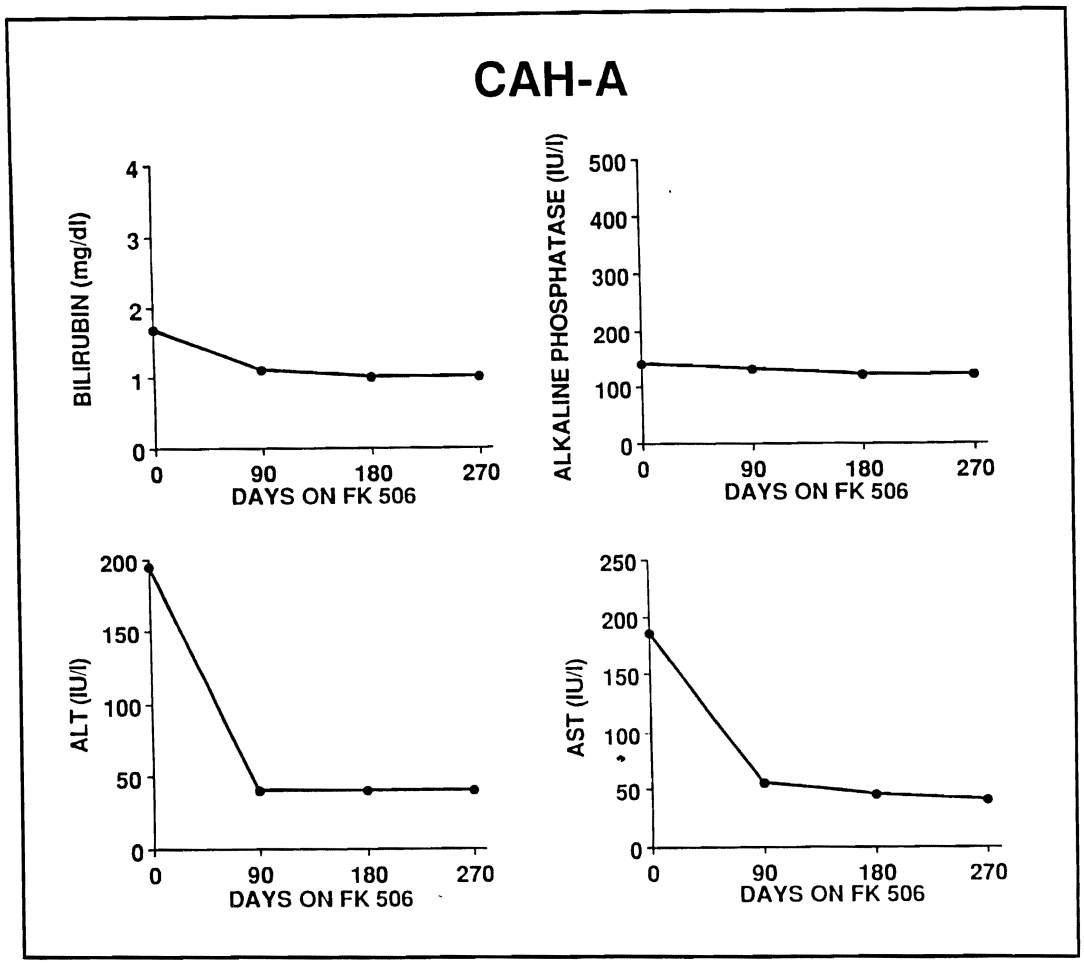

Fig. 10.8.4. Biochemical responses (serum total bilirubin, alkaline phosphatase, ALT and AST levels) in a representative responder with CAH-A treated with tacrolimus (FK506). Reproduced from Jhanson AW et al. Springer Semin Immunopathol 1993; 14:323-344.

Psoriasis

The results of treatment of psoriasis with tacrolimus (n = 16) have been quite rewarding.[26] All patients have shown a dramatic response to treatment—some with rapid clearing, while others take months to show clearing of the disease. Disease remission is associated with reductions in activated T cells,[27] selective inhibition of cytokine gene expression[28,29] and reduced adhesion molecule expression.[30] The renal toxicity of the drug appears to limit the ability to achieve remissions in some patients, especially in those who have received prior treatment with methotrexate. Combination therapy may be required in some of these subjects, and may limit the toxicities of single agents used in comparatively large doses.

Pyoderma Gangrenosum

The results of treatment of pyoderma gangrenosum (n = 6) with tacrolimus are promising.[31,32] One patient who was chronically steroid-dependent since childhood, with multiple steroid-induced complications, was able to suspend the use of steroids for the first time in his life. Four out of 6 patients achieved total remissions and 1 significant partial remission was obtained. One patient who did not respond to CsA was also refractory to tacrolimus and interestingly, showed in vitro evidence of lymphocyte resistance to the drug up to 100 ng/ml.

Multiple Sclerosis

More than 100 patients with chronic progressive multiple sclerosis (MS) have been treated beyond 1 year with tacrolimus in a 3 year protocol. Patients with both severe and mild disabilities have been treated, so the group is heterogenous. Some patients who received tacrolimus for transplants and who coincidentally, had MS, appear to have shown objective improvements over time. The neurotoxicity of the drug may be more limiting in this condition than in other autoimmune disorders. Although it is too early in the course of treatment to assess the effect of tacrolimus on disease progression, the side effects of tacrolimus were mild and the overall degree of disablility did not deteriorate significantly in 19 patients studied over 12 months.[33]

New Onset Type-I Diabetes Mellitus

A pilot study examined the capacity of tacrolimus to induce complete remission in new onset type I diabetes. Thirteen patients aged 23.5 ± 2.8 years with

duration of diabetes symptoms 19.1 ± 2.4 days, weight loss 5.9 ± 1.1% and insulin treatment 6.2 ±1.2 days were treated with oral tacrolimus (0.3 mg/kg/day). All patients had ketonuria but only 1 had mild ketoacidosis (HCO_3 < 18) at presentation. Four (31%) had noninsulin requiring remission at 4-6 months on tacrolimus treatment. Every patient with remission had stimulated C-peptide > 0.6 pmol/ml. This was not predictive since some patients with this level of C-peptide did not have remission. Only 1 patient with remission had a non-diabetic oral glucose tolerance test on tacrolimus. Remission was very short-lived (< 4 months) with no precipitating event or loss of C-peptide to explain recurrent hyperglycemia. There was no improvement of glycemia or reduction of insulin dose when tacrolimus was decreased. When the drug was discontinued, some patients lost C-peptide. Subjective side effects included headache and muscle cramps. There also were reversible, dose-related rises in serum creatinine, hyperkalemia and hypertension. Since in contrast to previously reported studies on CsA, tacrolimus did not induce long term remission in new onset type I diabetes, this may imply that in patients with a low β-cell mass, the drug is more diabetogenic than CsA. Low dose tacrolimus that can minimize toxicity can preserve C-peptide secretion.

Nephrotic Syndrome

Experience in treating steroid-resistant nephrotic syndrome (n = 32) with tacrolimus monotherapy has demonstrated three distinct patterns.[34,35] The three groups are approximately equally divided. Some patients experience a rapid reduction in proteinuria to normal or near normal values within weeks of initiating therapy. Others respond partially to tacrolimus alone, with reduction of protein excretion to approximately 50% of pretreatment values. The third group has demonstrated no change in protein excretion and has progressed to end stage kidney disease. The majority of patients treated to date have had focal sclerosing glomerulonephritis (FSGS) as the cause of steroid-resistant nephrotic syndrome. This, and the other histologic lesions treated in the study, tend to be resistant to essentially all forms of therapy and tend to progress to end stage renal disease. Partial and total unresponsiveness to tacrolimus may reflect that mediation of FSGS and other glomerulopathologies in these patients lies distal to IL-2 activation. In these cases, addition of other immunosuppressive agents which affect the more distal elements might improve the efficacy of tacrolimus. The use of anti-B cell agents, such as cyclophosphamide in combination with tacrolimus (recently described in murine SLE, see previous chapter), would seem to be a rational choice, as would the use of small doses of prednisone in patients refractory to tacrolimus alone.

The nephrotoxicity of tacrolimus has been the primary limiting factor in the treatment of these diseases. Like CsA, tacrolimus causes acute, dose-dependent rises in serum creatinine. Renal function improves with dosage reduction. The starting dose of tacrolimus has been reduced progressively from 0.15 mg/kg/day, given twice, to approximately 1/3 of this dose. Whether this approach will lessen the efficacy of tacrolimus is yet to be determined. No evidence of chronic tacrolimus toxicity has been observed in any of the patients treated for nephrotic syndrome, even at the highest drug dose.

SIDE EFFECTS OF TACROLIMUS IN HUMANS

Side effects of tacrolimus and CsA observed both in transplant and autoimmune disease patients are shown in Table 10.8.4. Adverse effects associated with the use of tacrolimus in transplant patients have recently been reviewed.[36] Adverse reactions requiring treatment or tacrolimus dose reduction are impairment of renal function (due in part to decreased glomerular blood flow), alterations in glucose homeostasis (a 15% incidence of new onset insulin-requiring diabetes has been observed in tacrolimus-treated transplant patients but none in autoimmune disease patients treated with tacrolimus as a single agent) and

Table 10.8.4. Potential side effects of tacrolimus and CsA in humans

Similarities
Decreased glomerular blood flow
Elevated serum potassium (? reduced aldosterone sensitivity of renal tubules)
De novo hypertension (CsA > tacrolimus)
Lymphoproliferative disease*
Nephrotoxicity
Neurotoxicity
Diabetogenicity
Decreased bone mineralization **(in vitro)
Steroid-sparing (tacrolimus > CsA)
Differences
Hirsutism (CsA; not tacrolimus)
Gum hypertrophy (CsA; not tacrolimus)
Hyperlipidemia (CsA)
Hypocholesterolemia (tacrolimus)
Elevated 1,25-$(OH)_2$ D levels (CsA; not tacrolimus)

* Reported in transplant patients
** Tacrolimus data based on in vitro observations only
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neurotoxicity. Amongst the benefits of tacrolimus compared with CsA are a lower incidence of de novo hypertension and the absence of gum hypertrophy and hirsutism. The frequency of side effects noted in autoimmune patients is shown in Table 10.8.5. A 1.6% incidence of posttransplant lymphoproliferative disorders has been observed in UPMC tacrolimus-treated transplant patients. No lymphoproliferative disorders have been reported from the tacrolimus treated autoimmune disease patient population (mean follow up time > 36 months).

AN INTELLIGENT DOSING SYSTEM FOR INDIVIDUALIZING TACROLIMUS THERAPY IN AUTOIMMUNE DISEASE

The accuracy and precision of an intelligent dosing system (IDS) for tacrolimus in predicting doses to achieve target drug levels has been prospectively evaluated both in transplant and autoimmune disease patients.[37] For dose individualization, the knowledge base is updated with patient-specific feedback, including the current dose, drug level and the new target level. The study population of 147 patients consisted of 97 transplant patients (liver and kidney) and 50 patients with autoimmune disorders. Patients in the transplant study group were entered sequentially and followed as a cohort. Patients in the autoimmune study group were randomly assigned to one of three predefined tacrolimus concentration windows (low, 0.1-0.3; medium, 0.4-0.7; and high, 0.8-1.3 ng/ml) as part of a concentration-controlled clinical trial. Predictions of steady-state plasma drug levels were made throughout the clinical course of autoimmune disease patients and during the first 6 weeks post-transplant in liver and kidney recipients. Tacrolimus concentration in plasma was measured by a monoclonal antibody-based ELISA assay. Accuracy was computed as the mean prediction error (mpe). Precision was computed as the root mean squared prediction error (rmspe). The accuracy of the IDS in each study group was as follows: 0.016 ng/ml (liver), 0.034 ng/ml (kidney), and -0.022 ng/ml (autoimmune). Because the 95% confidence interval included zero in each case, the IDS showed no bias. The precision of the IDS in each study group was as follows: 0.133 ng/mL (liver), 0.1903 ng/mL (kidney), and 0.1188 ng/mL (autoimmune). These results indicate that the tacrolimus IDS is both accurate and very precise (reproducible) both in transplant and autoimmune patients.

Table 10.8.5. Laboratory indices and side effects in 64 tacrolimus-treated autoimmune disease patients (University of Pittsburgh Medical Center)

(a)

Parameter	Baseline	3 Months	6 Months
Serum creatinine (mg/dl)	0.95 ± 0.38	1.16 ± 0.39	1.24 ± 0.44
BUN (mg/dl)	13.0 ± 5.4	17.8 ± 6.6	20.3 ± 9.0
Tacrolimus dose (mg/day)	8.5 ± 5.5	8.3 ± 5.6	7.8 ± 5.2
Tacrolimus plasma level (ng/ml)	-	0.54 ± 0.31	0.62 ± 0.47
Glucose (mg %)	106 ± 39	112 ± 41	108 ± 38
Hematocrit (%)	40 ± 6	37 ± 5	38 ± 5
Potassium meq/l	4.2 ± 0.5	4.5 ± 0.4	4.4 ± 0.4

Normal adult ranges: serum creatinine 0.5-1.4 mg/dl; BUN 5-20 mg/dl; glucose 65-115mg%; hematocrit 42-50%; potassium 65-115 meq/l.

(b)

Effect	Months After Treatment: Prevalence of Effect 3 Months	6 Months
Need for anti-hypertensive medication (baseline 15.9%)	25.4%	34.9%
Headache	38.5%	37.5%
Insomnia	33.3%	30.0%
Tremors	42.5%	42.5%
Hyperesthesia	33.3%	30.0%

Sixty-four tacrolimus-treated autoimmune disease patients (age 39.7 ± 15.2 years; 32M:32F).
Six months minimum follow-up for each patient.
The primary disease was as follows: Autoimmune inner ear disease 3; Behcet's syndrome 1; CAH-A 10; Corneal Tx (ophthalmology) 1; Diabetes type-I 5; Epidermolysis bullosa 1; Inflammatory bowel disease 3; Multiple sclerosis 20; Nephrotic syndrome 4; Scleritis 1; PBC 5; PSC 2; Psoriasis 5; Pyoderma gangrenosum 1; Scleroderma 2.

PROSPECTS FOR DRUG COMBINATION THERAPIES

In addition to tacrolimus monotherapy, the potential exists for drug combination therapies in autoimmune disease using tacrolimus in combination with other novel or well-established classes of immunosuppressive agents which act by mechanisms different from tacrolimus or CsA. Experimental combination therapies which are currently envisaged (e.g., for psoriasis or rheumatoid arthritis) include tacrolimus together with an antiproliferative agent, such as methotrexate, cyclophosphamide or the purine biosynthesis inhibitor mycophenolate mofetil, a prodrug of mycophenolic acid.

CONCLUSIONS

Although it is too early to draw firm conclusions about the value of tacrolimus in human autoimmune disease from the limited clinical investigations which have been undertaken to date, preliminary observations are encouraging. There is no doubt that tacrolimus is at least as efficacious an immunosuppressant as CsA. Its capacity (unlike CsA) to reverse allograft rejection suggests that it may be more broadly effective than CsA in autoimmune disease and may be useful in patients unresponsive to high dose steroids and/or other forms of immunosuppressive therapy. Further studies must include dose range and long term evaluation of tacrolimus therapy. Because tacrolimus augments hepatic repair and regeneration, it may prove especially valuable in patients with autoimmune liver disease. Although tacrolimus and CsA share several potential side effects, including nephrotoxicity, tacrolimus is less apt to induce hypertension and does not cause gingival hyperplasia or hirsutism at all. Amongst the beneficiaries of tacrolimus therapy have been children with nephrotic syndrome, in which prior high dose steroids have been discontinued. The inclusion of tacrolimus on the limited list of immunosuppressive drugs available for use in selected human autoimmune diseases appears justifiable.

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