Tacrolimus

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Contents

Core Messages

- Tacrolimus inhibits T cell activation and differentiation.
- Efficacy of tacrolimus was documented in experimental and clinical studies of uveitis.
- The favourable profile of adverse effects permits long-term use in uveitis patients.

31.1 Mechanism of Action and Pharmacokinetics

Tacrolimus, also known as FK-506, is produced by *Streptomyces tsukubaensis* and was discovered in Japan in 1984 [8]. The major target of tacrolimus is the T lymphocyte, by inhibiting T cell activation and cell proliferation via suppressing production of growth factor interleukin 2 (IL-2) and subsequent downregulation of IL-2 receptor on cell surface. T cells become activated following ligation of the T cell receptor (TCR) in the immunological synapse generated by receptor-ligand interactions including MHC molecules and co-accessory molecules on antigen-presenting cells (dendritic cells, macrophages and B cells). Subsequent signalling events in T cells include activation of cytoplasmic calcineurin. Calcineurin dephosphorylates and activates the transcription factor NF-AT, which regulates the production of proteins required for T cell activation and differentiation, e.g. cytokines, in particular IL-2 [20]. This process can be inhibited

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by blocking the phosphatase activity of calcineurin by a complex consisting of tacrolimus bound to the immunophilin protein FKBP12 (FK-506 binding protein). In addition to the inhibition of T cell signalling, tacrolimus appears to affect dendritic cell function by interfering with MHC class II-restricted antigen presentation after binding to another FKBP [4]. There are various isoforms of FKBP with a cell type-specific expression pattern, which might also explain the side effect profile of tacrolimus [9].

After oral administration of 0.3 mg/kg, the mean time to peak concentration ranges from 1.5 to 2.3 h. This time depends on the patient population studied and concomitant food intake with high-fat meals showing the most pronounced effect. The rate and extent of absorption were greatest under fasted conditions [25]. In the blood, tacrolimus is largely protein bound (albumin) or associated with erythrocytes. Tacrolimus is metabolised in the liver via the cytochrome P-450 system (P-450 3A4) and excreted in the bile. Monitoring of blood concentrations is required, since the metabolism varies between individuals and races [24]. Clearance is mainly observed through faecal elimination; thus, severe hepatic dysfunction does and renal insufficiency does not affect the excretion of tacrolimus [25]. Given the metabolism through the liver P-450 cytochrome systems, several drugs, such as calcium channel blockers, macrolides and anticonvulsants, as well as grapefruit juice may alter tacrolimus concentrations (Table 31.1) [25].

Table 31.1 Drugs with clinically relevant pharmacokinetic interactions with tacrolimus

Antibiotics	**Calcium channel blockers**
Clarithromycin	Diltiazem
Erythromycin	Nicardipine
Troleandomycin	Nifedipine
Rifabutin	Verapamil
Rifampin	**Others**
Chloramphenicol	Bromocriptine
Anticonvulsants	Cimetidine
Carbamazepine	Cyclosporine
Phenobarbital	Danazol
Phenytoin	Ethinyl estradiol
Antimycotics	Methylprednisolone
Clotrimazole	Metoclopramide
Fluconazole	Nefazodone
Itraconazole	Omeprazole
Ketoconazole	Sirolimus
Voriconazole	

31.2 Side Effects

The safety profile of tacrolimus was assessed in several studies on patients receiving transplants or being treated for autoimmune conditions. The most frequent adverse effects were headache, tremor, diarrhoea, nausea, hypertension and impaired renal function [25]. Some of these symptoms might be dose dependent. The nephrotoxicity of tacrolimus appears to be similar to cyclosporine A [9]. A meta-analysis revealed that the risk for hypercholesterolaemia after 1 year of treatment with tacrolimus is significantly lower in comparison to cyclosporine A [27]. A serious side effect of tacrolimus is insulin-dependent diabetes with an estimated relative risk of 2.56 after 6 months of treatment [27]. Blood glucose levels should be closely monitored since a substantial fraction of patients also receives steroids for additional immunosuppression. Tacrolimus is transferred across the placenta, but there are no adequate studies of tacrolimus during pregnancy. The use of tacrolimus in pregnant women has been associated with neonatal hyperkalaemia and renal dysfunction [25].

Table 31.2 lists the adverse effects of tacrolimus previously seen in uveitis studies (RCT and cohort studies). These patients were at lower doses and trough levels of tacrolimus in comparison to the transplantation studies, and, thus, the side effect profile may differ from these studies. The most frequent adverse effects observed in uveitis patients were neurological affecting approximately one third of the patients. Mean arterial pressure and serum cholesterol levels were found to be higher in patients treated with cyclosporine A than in patients treated with tacrolimus [16]. A long-term study on tacrolimus in uveitis patients estimated the overall risk for discontinuation of tacrolimus due to intolerance

Table 31.2 Adverse effects documented in uveitis patients treated with tacrolimus

Nervous system	**Gastrointestinal**
Headache	Nausea
Tremor	Diarrhoea
Paraesthesia	Abdominal pain
Anxiety/depression	Deranged liver function
Insomnia	**Urogenital**
Fatigue	Impaired renal function
Metabolic	**Miscellaneous**
Hypomagnesaemia	Chest pain
Hyperglycaemia	Alopecia
Haematological	Hirsutism
Lymphopaenia	Rash
Cardiovascular	Myalgia
Hypertension	Arthralgia

as 0.13/PY, which is lower than with cyclosporine A [3].

31.3 Experimental and Clinical Data for Uveitis

Although tacrolimus was mainly investigated in transplantation studies [26], the first report on its immunosuppressive activity in experimental autoimmune uveoretinitis (EAU) already appeared in 1988 [6]. Subsequent experimental studies on uveitis revealed that tacrolimus interferes with T cell activation, increases the recruitment time of cytotoxic T cells [17], inhibits CD4+ lymphocyte adhesion to retinal pigment epithelial cells [11] and induces upregulation of neurotrophic factor-related gene expression in EAU [19]. Investigation of S-antigen-induced uveitis in primates confirmed the immunosuppressive activity of tacrolimus described in these reports [2]. Studies in other models of autoimmune diseases further extended the understanding of the molecular processes induced by tacrolimus [12].

Several studies investigated different routes of administration of tacrolimus in experimental uveitis models: intravitreal injection [18], scleral plugs [22] and eye drops with liposome-encapsulated tacrolimus [28]. Although these experiments demonstrated the immunosuppressive efficacy of locally administered tacrolimus, these methods have not yet been transferred to clinical practice.

There are only few trials investigating the clinical efficacy of tacrolimus in uveitis patients. Major studies are listed in Table 31.3. The first clinical trial of tacrolimus in uveitis was performed in Japan with the majority of patients having had Behçet's disease [13, 14]. A report from 1993 on 53 patients documented the dose-dependent increase of clinical efficacy of tacrolimus in the range of daily doses between 0.05 and 0.2 mg/kg [15]. Another Japanese study involved 16 patients with noninfectious posterior uveitis of whom 10 had a decrease in the recurrence rate and inflammatory activity, respectively, after initiation of immunosuppression with tacrolimus [5]. These results were confirmed by a UK study on 6 patients [23].

Low-dose tacrolimus (<0.1 mg/kg) in combination with low-dose prednisolone was shown to be effective to maintain visual acuity and reduce ocular inflammation in cyclosporine A-refractory posterior uveitis [7]. Based on these findings, we performed a randomised controlled trial (RCT) of tacrolimus versus cyclosporine A therapy [16]. Thirty-seven patients with chronic sight-threatening posterior uveitis were randomised to either tacrolimus or cyclosporine A. These patients were previously given unacceptably high doses of prednisolone, repeatedly required a high-dose steroid rescue for recurrent disease or had severe sight-threatening intraocular inflammation that required immediate initiation of high-dose prednisolone and a second-line agent. Thirteen of the 19 patients (68 %) given tacrolimus responded to treatment defined as an improvement of log-MAR visual acuity by at least 0.2 or a decrease of the binocular indirect ophthalmoscopy (BIO) score to 0 within 3 months after initiating therapy. There was no significant difference in the response rate in the tacrolimus group as compared to the cyclosporine A group. The clinical response in patients to either drug was accompanied by a significant decrease of CD4+ T cell expression of the proinflammatory cytokine TNFα in contrast to nonresponders. These findings are consistent with the known mechanism of action of calcineurin phosphatase inhibitors.

Table 31.3 Design and outcome of selected studies on Tacrolimus in the treatment of uveitis

Authors (year)	Type of study	Subtype of uveitis	No. of patients	Previous treatment	Dosing regimen	Outcome	SE
Mochizuki et al. (1991) [14]	RCR	Predominantly BD	53	nr	0.05–0.2 mg/kg	Dose dependent, up to 83 % efficacy	28 % renal impairment, 13 % hyperglycaemia
Murphy et al. (2005)[16]	RCT	Miscellaneous PU and IU	19	CS, 2nd-line agents	0.03–0.08 mg/kg	13/19 patients responded No significant difference to CsA with respect to response	63 % of patients
Lee et al. (2002) [10]	RCT	Miscellaneous PU and IU that could achieve remission	58	CS tapering dose to 10 mg	0.03–0.08 mg/kg	35/58 patients entered prednisolone induced remission, monotherapy: 62.5 %; dual therapy: 68.4 %, no difference in outcome between 16 patients on Tac monotherapy or 19 patients on dual therapy	Greater degree of drug intolerance in dual therapy group, all failures in monotherapy group were disease reactivation
Hogan et al. (2007) [3]	RCR	Miscellaneous PU and IU	62	CS, 2nd-line agents	3 mg/day	61 % chance to discontinue steroids after 2 years	0.13/PY discontinuation rate due to intolerance

CsA cyclosporin A, *PU* posterior uveitis, *IU* intermediate uveitis, *RCT* randomised controlled trial, *Tac* tacrolimus, *BD* Behçet's disease, *PY* patient year, *nr* not reported, *RCR* retrospective case review, *SE* side effects, *CS* corticosteroids

The long-term efficacy of tacrolimus was recently evaluated in two studies. The first investigation included 62 patients with mostly posterior and idiopathic forms of uveitis [3]. The median total daily tacrolimus dose was 3 mg and, importantly when comparing to other studies, at median trough levels of 5.2 ng/ml. The efficacy of tacrolimus in controlling uveitis activity was primarily assessed by the successful tapering of prednisone, which was achieved in a substantial fraction of patients. There was a 61 % chance to discontinue steroids after 2 years of treatment with tacrolimus. Patients successfully tapered their oral prednisone to 10 mg daily at an average rate of 1.62 per patient year (PY), with an 85 % probability of achieving ≤10 mg/day after 1 year 2 months of treatment. Although alternative second-line agents had to be added to the treatment regimen, especially when the prednisone dose was below 10 mg/day, there was a significant improvement in visual acuity during the treatment with tacrolimus. A second prospective study involved 11 patients with posterior uveitis [1]. The mean follow-up was 45 months. In 6 patients, tacrolimus proved to be sufficient as a single agent in the long-term control of intraocular inflammation.

Currently, there are no reports of RCT comparing tacrolimus to other classes of immunosuppressives or placebo in the treatment of uveitis. There is however a recent report to show that there was no difference between low-dose prednisolone and tacrolimus (dual therapy) and tacrolimus alone (monotherapy) in patients who had achieved remission with tapering high-dose prednisolone [10]. Out of 58 patients recruited, 35 patients successfully tapered their prednisone to 10 mg daily. Of these, 16 were allocated randomly to receive tacrolimus monotherapy, and 19 to continue taking prednisone and tacrolimus dual therapy. The difference in the mean change in VA for monotherapy compared with the dual therapy group was less than 1 logMAR letter (logMAR, −0.008; 95 % confidence interval, −0.108 to 0.092; $P=0.870$). The proportion of patients who tolerated treatment and maintained disease remission for 9 months after randomisation also was similar in both groups (monotherapy, 62.5 %; dual therapy, 68.4 %; $P=0.694$). All monotherapy treatment failures were the result of disease reactivation, whereas 50 % of dual therapy failures were the result of drug intolerance.

31.4 Indication and Dosage for Uveitis

The indications for tacrolimus are to assist in the management of non-infectious uveitis where inflammatory control cannot be achieved with doses of prednisone below 10 mg/day. The immunosuppressant can be added with others such as anti-metabolites and anti-proliferative agents such as methotrexate and mycophenolate mofetil, respectively. As such some patients may be on 'triple' therapy prior to further escalation to 'biologics' therapy. Tacrolimus should not be used with other calcineurin inhibitors (e.g. cyclosporin).

In general to reduce any adverse co-morbidity, tacrolimus should be used with care in patients over 55 years of age because of the increase risk of renal impairment and hypertension, and avoided where possible in patients with pre-existing renal impairment, hypertension and diabetes. Caution is also needed in patients with malignancy and liver impairment.

For control of uveitis, doses should initially start at 0.03 mg/kg/day increasing to 0.08 mg/kg/day in 2 divided doses.

Doses should be increased in 1–2 mg/day steps, repeating blood trough levels 2 weeks later, where trough levels of 5–10 μg/l are optimal. Trough levels are measured 12–14 hours post-dose and when stable checked monthly thereafter.

Routine monitoring should include: blood pressure, weight, urinalysis, electrolytes and creatinine, hematology and liver function tests monthly, with lipid profile and serum magnesium every 3 months.

31.5 EBM Grading

The previously reported non-randomised studies were of sufficient quality to classify the evidence for tacrolimus being effective in uveitis as type IIA [21]. Tacrolimus was also used as a second- or third-line agent in several clinical trials of new

immunosuppressive drugs, such as anti-TNF agents. Due to the heterogeneity of patient populations, the data from these trials are not sufficient to draw conclusions about the role of tacrolimus in combination therapies with these agents.

Take-Home Pearls

- Tacrolimus has a place as a steroid-sparing agent in the treatment of uveitis.
- Monitoring of blood concentrations and adverse effects is necessary during therapy.

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