



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Tacrolimus

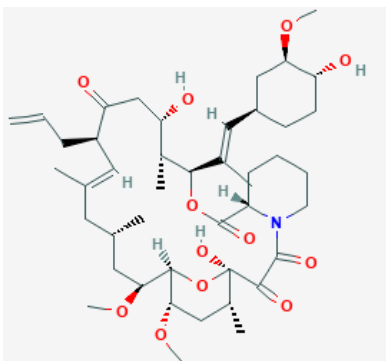
Evidence Summary

Tacrolimus is an immunosuppressant which may have neuroprotective properties, but use requires constant monitoring for elevated levels, which result in toxicities to several organ systems.

Neuroprotective Benefit: Inhibiting calcineurin activity in the context of overactivation may restore synaptic plasticity, and mitigate neuroinflammation. Sustained benefits to cognition may be limited by a very narrow therapeutic window.

Aging and related health concerns: Tacrolimus may help promote tolerance for some autoimmune diseases, but risk for toxicities limits use.

Safety: The pharmacokinetics vary widely across patients, leading to increased risk for nephrotoxicity, neurotoxicity, and cardiotoxicity in some people depending on their genetic variants of metabolizing enzymes. Tacrolimus also increases the risk for diabetes.

<p>Availability: Rx</p>	<p>Dose: Depends on formulation, and metabolic profile of an individual. Dosage based on achieving blood trough concentration within therapeutic range (generally 5-20 ng/mL)</p>	<p>Chemical formula: C₄₄H₆₉NO₁₂ MW: 804.0 g/mol</p>  <p>Source: PubChem</p>
<p>Half-life: 12 hours (range 3.5 to 40.5 hours) in transplant patients</p>	<p>BBB: Penetrant</p>	
<p>Clinical trials: Tested extensively in RCTs for organ transplant, and in some autoimmune conditions</p>	<p>Observational studies: One study (n=2,644) showed potential for reduced risk for dementia, numerous studies examine genetic associations of pharmacokinetics, and risk factors for tacrolimus-induced toxicities.</p>	

What is it?

Tacrolimus (FK506) is an immunosuppressant that is used to prevent rejection in the context of organ transplant. It is currently approved for use in kidney, liver, and heart transplant [1]. It is available as an immediate release formulation (Prograf®), as well as extended-release formulations (Astagraf XL® and Envarsus XR®). A topical formulation (Protopic®) is approved for short-term use as a second-line therapy for atopic dermatitis. Tacrolimus binds to and acts as a co-receptor for FK506-binding proteins (FKBPs), which are immunophilins. This complex negatively impacts immune cell activation, and thus acts as an immunosuppressant. Although tacrolimus can bind multiple FKBP, its primary mode of action involves the binding of FKBP12 [1]. This complex binds to the calcium calmodulin-dependent phosphatase, calcineurin, and inhibits its activity. This blocks the dephosphorylation of the transcription factor, nuclear factor of activated T-cells (NFAT). By blocking the activation of NFAT, tacrolimus inhibits the synthesis of the cytokine IL-2, which is involved in T-cell proliferation. Inhibiting the first stage of T-cell activation can induce a state of immunogenic tolerance, which is beneficial in the context of organ transplant recipients to prevent immunological rejection. Tacrolimus has also been tested in a variety of autoimmune conditions for its tolerance promoting properties. Proper calcium regulation is essential for brain activity, and the dysregulation of calcium-regulated enzymes is implicated in neurological



dysfunction [1]. Consequently, tacrolimus is also being investigated for its neuroprotective potential based on its ability to inhibit calcineurin.

Neuroprotective Benefit: Inhibiting calcineurin activity in the context of overactivation may restore synaptic plasticity, and mitigate neuroinflammation. Sustained benefits to cognition may be limited by a very narrow therapeutic window.

Types of evidence:

- 1 observational study of calcineurin inhibitor use for transplant and dementia risk
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

A retrospective observational study including 2,644 organ transplant patients treated with the calcineurin inhibitors tacrolimus or cyclosporine found that the transplant patients had a lower incidence of dementia relative to the general population [2]. 22.2% (n=587) of their patient population was over age 65, and only six patients were diagnosed with dementia, or 1.02% of the population. The prevalence in this population was significantly lower than the general population, 10.13%, based on the Alzheimer's Association Facts and Figures for 2014. Furthermore, this population is expected to be at higher risk due to the high prevalence of known dementia risk factors, such as diabetes and cardiovascular disease. The mechanism underlying this potentially protective effect has not been established, but is hypothesized to involve immune regulation and calcineurin modulation in the CNS.

Human research to suggest benefits to patients with dementia:

There are currently no studies to indicate benefit to patients with dementia, though a registered pilot open-label clinical trial ([NCT04263519](https://clinicaltrials.gov/ct2/show/study/NCT04263519)) testing tacrolimus in patients with mild cognitive impairment (MCI) may provide some evidence. A systematic gene analysis of brain tissue (n=544) identified 12 drugs predicted to restore the aberrant gene expression seen in the brains of patients with Alzheimer's disease (AD) [3]. Tacrolimus was one of the drugs identified in this study.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:**Alzheimer's disease: POTENTIAL BENEFIT FOR NORMALIZATION OF CALCINEURIN ACTIVITY**

Tacrolimus has been tested in a variety of Alzheimer's disease (AD) models. The effects were generally similar with respect to synaptic plasticity and A β pathology, however there was a lack of consistency on cognitive measures. The lack of efficacy was generally attributed to insufficient dosing. Determination of the optimal dose for AD is one of the major barriers for the repurposing of tacrolimus. The therapeutic window for neuroprotective activity is projected to be very narrow, which is further complicated by the fact that tacrolimus is known to have very high interindividual variability in bioavailability as measured by tissue and circulating levels. A biomarker is needed that is linked to its neuroprotective activity and can be used to guide therapeutically appropriate dosing.

Synaptic plasticity: Calcium homeostasis has been found to be disrupted in a variety of neurodegenerative diseases [4]. The balance between calcium-dependent kinases and calcium-dependent phosphatases is critical for the maintenance of synaptic plasticity mechanisms. Calcineurin is the major calcium-dependent phosphatase in neurons, and thus plays a major role in this process. A study using postmortem brain tissue found that there was a 50% increase in levels of truncated calcineurin A in the AD brain, and that the activity was increased nine-fold in the presence of Ca²⁺/calmodulin in the AD brain, relative to a two-fold increase in activity in the control brain [5]. This suggests that calcineurin activity may be aberrantly increased in the AD brain.

In postmortem brain tissue (n=18), the enzyme, p(Thr286)CaMKII, which is critical for activity-dependent synaptic remodeling, was found to be re-localized from the dendrites to the cell body in the context of AD [6]. The alteration in p(Thr286)CaMKII expression in the hippocampal dentate gyrus was correlated with cognitive performance on the Mini-Mental State Exam (MMSE) (MCI r = -0.540, p < 0.05; D; AD r = -0.527, p < 0.05). In mice, intracerebroventricular injection of A β reduced hippocampal levels of p(Thr286)CaMKII, which was rescued by treatment with tacrolimus. The protective effect was attributed to the inhibition of calcineurin.

Reduction of calcineurin activity (by 31.85 \pm 5.04%) was also seen in conjunction with higher levels of the synaptic markers synaptophysin and PSD95 in 8-month-old APP/PS1 mice treated with tacrolimus (5 mg/kg i.p. every 2 days) for two months [7]. Seven days of tacrolimus (100 mg/kg i.p.) treatment also restored spine density in APP/PS1 mice, but did not impact spine length or dystrophic swellings. Tacrolimus (100 mg/kg i.p. for 4 days) also led to a normalization of dendritic spine density in the cortex in humanized ApoE4 mice [8]. The effects were seen in both E3/E4 heterozygotes with a 36.6% decrease



in calcineurin activity and 9.3% increase in spines, and in E4/E4 homozygotes with a 64.2% decrease in calcineurin and 30.6% increase in spines. An increase in spine density and dendritic arbor complexity was also seen in healthy adult mice (6-8 months old) at a dose (100 mg/kg i.p.) known to reach brain tissue levels of around 300 ng/g in rodents [9]. While these changes may be beneficial in the context of AD, the structural synaptic changes in otherwise healthy brains could be a potential mechanism for the neurological side effects seen in approximately 10% of tacrolimus-treated transplanted patients. In the Tg2576 AD model, acute treatment with tacrolimus (10mg/kg i.p.) rescues synaptic plasticity by promoting the maintenance of glutamate receptors at synaptic sites [10]. Tacrolimus also restored synaptic scaling and trafficking of glutamate receptors in hippocampal neurons carrying the presenilin 1 M146V mutation [11]. The effects on synaptic plasticity are all mediated by tacrolimus's inhibition of calcineurin.

A β pathology: Changes in calcineurin and NFAT3 levels have been shown to be associated with A β 42 levels in postmortem hippocampal tissue, suggesting that calcineurin/NFAT inhibition may reduce A β levels. In the APP/PS1 model, treatment with tacrolimus (5 mg/kg i.p. for 2 months) reduced A β plaque burden, which was associated with an increase in the matrix metalloprotease MMP-9, which has been shown to degrade A β [7]. Plaque load was also reduced in this model when tacrolimus was administered at 1 mg/kg/day for 28 days via a mini-osmotic pump [12]. Additionally, tacrolimus (10 ppm in drinking water) reduced tau pathology in the P301S tauopathy model, when administered starting at two months of age [13]. The effects on pathology appear to be associated with the attenuation of microgliosis.

Immune regulation: NFAT activity is thought to play a role in driving A β -mediated neurotoxicity by inducing gliosis. Peripheral administration of tacrolimus (1 mg/kg/day) in AD mice reduced inflammatory cytokine levels (IL-6, TNF α , and IL-1 β) in the spleen, and reduced levels of CD68, a marker of activated microglia, in the hippocampus [12]. This resulted in a reduced A β plaque load, but did not significantly impact cognitive performance. An attenuation of astrogliosis, based on GFAP positivity, was seen in conjunction with reduced A β plaques following tacrolimus treatment (5 mg/kg) in the same AD model (APP/PS1) [7]. The mitigation of microglial activation and neuroinflammation was associated with a reduction in tau pathology when P301S tau mice were treated with tacrolimus prior to the onset of tau pathology [13].

Cognition: Effects on cognition have been mixed. The majority of studies that found changes on pathology, synaptic, or biochemical measures did not assess cognition. The discrepancies amongst studies that test cognition may be related to different dosing schemes. One study found that acute administration (10 mg/kg i.p. 12 hours prior to testing) improved performance on measures of intermediate and long-term memory on the novel object recognition task in AD (Tg2576) mice, but no

effects were seen on short-term memory or in wild-type mice [14]. Despite an attenuation of A β plaque load, tacrolimus treatment at 1 mg/kg/day for 28 days did not improve T-maze performance in APP/PS1 mice [12]. At a dose of 0.5 mg/kg, tacrolimus had no effect on Morris water maze performance in the streptozotocin-induced AD model in male rats [15], while a separate study found that a dose of 1 mg/kg improved performance on this test in this model [16]. It is unclear if these acute effects are transitory, or if they could be sustained with chronic dosing.

Brain Aging: POTENTIAL BENEFIT (Preclinical)

A study in middle-aged (5–8-year-old) Beagles examined the effect of tacrolimus (0.075 mg/kg twice a day) on higher-order diffusion MRI age-associated microstructural atrophy after one-year [17]. Tacrolimus was found to protect against microstructural alterations, but did not significantly impact age-related volumetric atrophy in the hippocampus. In this study, tacrolimus reduced hippocampal and parahippocampal neurite density index. It also protected against age-related increases in the parahippocampal orientation dispersion index, and decreases in the fractional anisotropy in the prefrontal cortex. This study is planned to continue for another year, which may help assess whether tacrolimus can inhibit cognitive decline as the dogs age.

Ischemic stroke: UNCLEAR BENEFIT (Preclinical)

In the rat middle cerebral artery occlusion (MCAO) model of transient focal cerebral ischemia, tacrolimus (1 mg/kg i.v.) reduced ischemic damage and markers of microglial activation in the cortex [18]. In a rat model of transient global cerebral ischemia (4-VO), tacrolimus treatment (1.0 mg/kg i.v.) beginning during the reperfusion period, and then subsequently at 6-, 24-, 48- and 72-hours post-injury (i.p.) reduced hippocampal damage, but did not prevent neurological impairments [19].

Parkinson's disease: POTENTIAL BENEFIT BUT NARROW THERAPEUTIC WINDOW (Preclinical)

In a rat model using alpha-synuclein overexpression (rAAV2/7 α -synuclein), tacrolimus (1 mg/kg/day i.v. for 4 weeks) reduced the infiltration of T-cells and the activation of microglia and macrophages [20]. Despite an increase in dopaminergic neuron survival, there were no significant improvements on behavioral measures. This study highlights the potentially narrow therapeutic window for tacrolimus in neurodegenerative conditions. At 0.5 mg/kg, there was no effect on neuronal survival. 1.5 mg/kg offered better survival, but small minor adverse effects on locomotor activity were noted, and levels above 2 mg/kg were not well-tolerated. Wide variability in the concentrations of tacrolimus in the cerebrospinal fluid (CSF) relative to the blood across animals further complicates the ability to dose at a safe and effective level.

APOE4 interactions: Not established

Aging and related health concerns: Tacrolimus may help promote tolerance for some autoimmune diseases, but risk for toxicities limits use.

Types of evidence:

- 1 meta-analysis of RCTs for tacrolimus in rheumatoid arthritis
- 2 meta-analyses of RCTs for tacrolimus in lupus nephritis
- 1 meta-analysis of RCTs for topical tacrolimus in atopic dermatitis
- 1 meta-analysis of RCTs and observational studies for tacrolimus in ulcerative colitis
- 1 meta-analysis of RCTs for tacrolimus in myasthenia gravis
- 1 observational study of tacrolimus use and Covid-19

Autoimmune disease

Tacrolimus is primarily used to prevent immune-mediated rejection of transplanted organs by inducing immune-tolerance. Although not approved for these indications, tacrolimus (oral) has been used as a second-line therapy for several autoimmune diseases to help promote immune tolerance to autoantigens. A topical form is approved for atopic dermatitis.

Rheumatoid arthritis: POTENTIAL BENEFIT

A meta-analysis of four RCTs found that at a dose of 1-2 mg/day, tacrolimus use was associated with a reduction in the American College of Rheumatology 20 composite score (ACR20) (Risk ratio [RR] 1.71 (95% confidence interval [CI] 1.20 to 2.42) [21]). The dose of 3 mg/day was associated with slightly better efficacy (RR 2.30, 95% CI 1.79 to 2.96).

Lupus nephritis: POTENTIAL BENEFIT

In comparative meta-analyses (12 RCTs), tacrolimus was not significantly more effective than mycophenolate mofetil [22; 23]. In one meta-analysis, tacrolimus was found to be more effective for achieving complete renal remission compared to intravenous cyclophosphamide therapy [23]. Similarly, a second meta-analysis found that tacrolimus plus glucocorticoids was more effective for partial and complete remissions, as well as lowering the levels of ds-DNA, relative to cyclophosphamide plus glucocorticoids [22].



Atopic dermatitis: BENEFIT FOR SHORT-TERM USE

In a meta-analysis of 14 RCTs (n=7376 adults and children) the calcineurin inhibitors, 0.3% or 0.1% tacrolimus and 1% pimecrolimus showed slightly higher efficacy relative to corticosteroids

(RR 1.24, 95% CI 1.06 to 1.44) [24]. However, when separated by potency, the calcineurin inhibitors were not more efficacious than mid- to high potency steroids, and had a worse safety profile.

Ulcerative colitis: POTENTIAL BENEFIT

A meta-analysis of two RCTs (n=103 participants) and three observational studies (n=831) found that tacrolimus improved two-week clinical response relative to placebo in RCTs (RR 4.61, 95% CI 2.09 to 10.17) [25]. The clinical response rate at three months (Event rate 0.76, 95% CI 0.59 to 0.87), and colectomy-free rate at 12 months (Event rate 0.69, 95% CI 0.50 to 0.83) were also high with tacrolimus use in the observational studies.

Myasthenia gravis: NO BENEFIT

A meta-analysis of five RCTs (n=683 patients) found that the use of tacrolimus for six months or 12 months was not associated with a reduction in the use of glucocorticoids in patients with myasthenia gravis [26].

COVID-19: POTENTIAL BENEFIT IN TRANSPLANT PATIENTS

In the ELITA/ELTR European Study including nine countries, factors associated with patient outcomes were assessed in liver transplant recipients with Covid-19 [27]. Age (>70) was the strongest predictor for a negative outcome, while the use of tacrolimus was associated with a positive effect on survival (Hazard ratio [HR] 0.55, 95% CI, 0.31 to 0.99).

Safety: The pharmacokinetics vary widely across patients, leading to increased risk for nephrotoxicity, neurotoxicity, and cardiotoxicity in some people depending on their genetic variants of metabolizing enzymes. Tacrolimus also increases the risk for diabetes.

Types of evidence:

- 3 meta-analyses or systematic reviews for topical tacrolimus safety
- 11 meta-analyses or systematic reviews for oral tacrolimus safety
- 4 FDA prescribing labels (Prograf®, Protopic®, Astagraf XL®, Envarsus XR®)
- 4 retrospective/observational studies on tacrolimus-related toxicities/outcomes
- 1 review on tacrolimus use and safety
- 8 studies on genetic associations and tacrolimus PK and/or toxicity
- 4 case reports of tacrolimus-associated toxicities

The [FDA label](#) for the topical form of tacrolimus, which is approved for atopic dermatitis contains a boxed warning that the long-term safety of calcineurin inhibitors has not been established, that rare cases of malignancies have been reported, and that long-term use should be avoided. A meta-analysis of 11 studies (n=408,336 in cohort studies, 17,924 in case control studies) found that topical calcineurin inhibitor use was not associated with an overall increased risk for cancer (Relative risk [RR] 1.03, 95% CI 0.92 to 1.16) or skin cancer (RR of 0.72, 95% CI 0.44 to 1.18), but increased risk for lymphoma (RR 1.86, 95% CI 1.39 to 2.49) [28]. A systematic review of five cohort studies and 18 case control studies assessed the relationship between lymphoma and atopic dermatitis [29]. An increased risk for lymphoma was seen in cohort studies (RR 1.43, 95% CI 1.12 to 1.81), but not in case control studies (Odds ratio [OR] 1.18, 95% CI 0.94 to 1.47). The severity of atopic dermatitis was associated with elevated lymphoma risk (OR range 2.4 to 3.72), suggesting that some of the reports of increased incidence of lymphoma with calcineurin inhibitors may have been confounded by an increased risk in this patient population.

A meta-analysis of 14 RCTs (n=7,376) found that the major adverse events associated with the use of topical calcineurin inhibitors were skin burning (RR 3.32, 95% CI 2.90 to 3.80) and pruritus (RR 1.59, 95% CI 1.34 to 1.80) [24].

The side effect profile of tacrolimus in transplant patients may be complicated by issues of multi-morbidity and polypharmacy in this population. The risk profile tends to show less toxicity when used in autoimmune conditions, but the risks are still significant. In a systematic review of 5 RCTs for myasthenia gravis found that most adverse events were mild [26]. Adverse events include infections, gastrointestinal events, and diabetes. In a systematic review of 18 studies in lupus nephritis found that

tacrolimus was associated with trends toward more new onset hypertension and hyperglycemia cases [23]. A meta-analysis of 4 RCTs for tacrolimus use in rheumatoid arthritis found that there was a trend toward more gastrointestinal disorders, and metabolic and nutritional disorders at a dose of 1-2 mg/day, and a significant increase, relative to placebo, at 3 mg/day (RR 1.81, 95% CI 1.32 to 2.48, $p < 0.001$; RR 2.50, 95% CI 1.26 to 4.96, $p = 0.009$; respectively)[21]. A post-marketing safety report of tacrolimus use for arthritis in Japan ($n=3172$) found that the most common adverse reactions were abnormal laboratory values (12.5%), gastrointestinal disorders (6.4%), infections and infestations (5.8%), metabolism and nutrition disorders (4.3%), and renal and urinary disorders (2.7%) [30]. Serious adverse drug reactions were observed in about 2.0% of participants, with serious infections occurring in approximately 1.0%.

The [FDA label](#) for tacrolimus contains several warnings for toxicity. The oral form, which is approved for organ transplant, contains a black box warning for malignancies and serious infections. There are also warnings for new onset diabetes, nephrotoxicity, neurotoxicity, hyperkalemia, hypertension, anaphylaxis, myocardial hypertrophy, and pure red cell aplasia.

New onset diabetes: A meta-analysis of 24 case control studies ($n= 7,140$ participants) found that tacrolimus use was associated with increased risk for new onset diabetes in renal transplant patients (OR 1.2, 1.02 to 1.41, $p=0.03$; 12 studies, $n=4409$ patients), though this risk was lower than other modifiable risk factors such as body mass index, , steroid use, and hepatitis B virus, as well as non-modifiable factors such as age and family history [31]. In a meta-analysis of 20 retrospective studies ($n=4,580$ participants), the use of tacrolimus was also found to be a risk factor for new onset diabetes in liver transplant patients (OR 1.34, 95%CI 1.03 to 1.76, $p = 0.03$) [32]. In comparison with cyclosporine, the use of tacrolimus in organ transplant was associated with a higher incidence of new onset diabetes (16.6% vs 9.8%) in a review of 56 studies. Similarly, a meta-analysis of 16 prospective studies ($n=3,043$ participants) showed a higher incidence of diabetes (10.4% vs 4.5%, $p < 0.00001$), in both renal (9.8% vs. 2.7% $p < 0.00001$) and non-renal transplant populations (11.1% vs. 6.2%; $p < 0.003$) [33]. A meta-analysis of five RCTs ($n=923$ participants) also found that tacrolimus was associated with a higher incidence of diabetes in renal transplant patients (RR: 1.79, 95% CI 0.98 to 3.27, $p = 0.06$), relative to cyclosporine [34].

Nephrotoxicity: Tacrolimus treatment has been shown to induce nephrotoxicity in 17 to 44% of kidney transplant recipients [1]. The risk is greater in patients treated with a higher dose (0.3 mg/kg). The toxicity can be acute or chronic. Acute nephrotoxicity is defined as a moderate rise in serum creatine level that is associated with an increase in blood levels of tacrolimus (>20 ng/mL) which is higher than the therapeutic target dose (8 to 10 ng/mL). It is reversible upon dose reduction or discontinuation.

Chronic nephrotoxicity is not reversible and may stem from a local accumulation of tacrolimus in the kidney, but the mechanism of toxicity is not well-understood.

Neurotoxicity: Tacrolimus use has been associated with neurotoxic symptoms, including tremor, headache, insomnia, hyperesthesia, and itching, as well as severe events, such as seizures, coma, dysarthria, and encephalopathy [35]. Neurotoxicity appears to be more common in liver transplant patients. A retrospective analysis of liver transplant patients (n=175) found that calcineurin-inhibitor induced neurotoxicity occurred in 21.4% of the transplant recipients in this study [36]. A retrospective study in adult renal transplant patients (n=57) found that 53% reported at least one neurological symptom with tacrolimus use, including tremors, headache, fatigue, itching, and insomnia, though they tended to be mild and improved with dose reduction [35]. Three patients experienced seizures, and two experienced severe myalgia. Toxicities tend to occur in the context of elevated tacrolimus levels. Although blood levels were within the therapeutic range, it was not examined whether CNS levels were elevated in these patients with severe neurological events. Differences in P-glycoprotein activity at the BBB may account for differential accumulation of tacrolimus in the brain across subjects [37]. Variations in tacrolimus accumulation in the CNS has been seen in animal studies [20]. Tacrolimus use has also been associated with optic neuropathy in case reports [38].

Cardiotoxicity: Tacrolimus-induced cardiotoxicity, such as myocardial hypertrophy, has primarily been reported in pediatric transplant recipients, though it is rare [39; 40]. The effects are generally reversible with discontinuation or dose reduction. There have also been some case reports of cardiotoxicity in adult transplant recipients [41].

Genetics: Tacrolimus is primarily metabolized by cytochrome P450 (CYP) 3A enzymes in the intestine and liver. Consequently, the capacity to metabolize tacrolimus is impacted by the levels of CYP3A enzymes CYP3A4 and CYP3A5 [42]. A genetic variant in CYP3A5 (6986A>G) greatly influences the circulating levels of tacrolimus levels by impacting its metabolism [43]. The expresser genotype CYP3A5*1 (A/A *1/*1 and A/G *1/*3) have more rapid metabolism of tacrolimus than those with the nonexpresser genotype CYP3A5*3 (G/G *3/*3). In those with CYP3A5*1, CYP3A5 accounts for approximately 50% of all CYP enzymes [44]. The CYP3A5*3 variant along with other variants (*6 and *7) encode for truncated proteins which may be non-functional. The *3 variant is the major allele in certain populations. For example, 80-85% of Caucasians are *3 homozygotes. Due to the differential metabolism, the trough concentration–dose ratio is lower for expressers (*1) relative to non-expressers [45]. As a result, clinical guidelines suggest that expressers receive higher doses than non-expressers, if the genotype is known [45]. If the concentration-dose relationship is not carefully monitored, expressers may be at higher risk for acute rejection, while non-expressers may be at higher risk for tacrolimus-



induced toxicities. A meta-analysis found that expressers had a higher rate of acute renal rejection in Asian populations (OR 1.62, 95% CI 1.16 to 2.24; 10 studies), but the effect was not significant in European populations (OR 1.12, 95% CI 0.83 to 1.52; 13 studies) [43]. In an observational study (n=322), although there were no statistically significant differences in posttransplant toxicities, there was a higher five-year mortality rate in those with the *3 allele, which may be related to higher tacrolimus exposure over time [44]. The impact of this allele may be lessened in the context of frequent dose-concentration monitoring and correction.

Brain levels of tacrolimus are impacted by changes in levels of the P-glycoprotein transporter. Single nucleotide polymorphisms (SNPs) in the ABCB1 transporter were found to be associated with risk for tacrolimus-induced neurotoxicity in liver transplant patients. [37]. The G2677[A,T] SNP in exon 21 was a positive predictor for neurotoxicity (coefficient 8.35), while the C3435T SNP in exon 26 was a negative predictor (coefficient -9.44).

Pharmacokinetics: Tacrolimus shows very high inter- and intra-individual variability in its pharmacokinetics. In general, there is a poor correlation between dose and blood concentrations in adults ($r^2 = 0.005-0.06$) [46]. In addition to CYP genetics, age impacts expression levels of CYP enzymes, such that pharmacokinetic variability increases in the elderly. One study found that tacrolimus levels in the peripheral blood mononuclear cells (PBMCs) of kidney transplant recipients was correlated with age, and that the levels were related to changes in the expression of CYP3A4 [42]. Changes to liver mass and function with age also impact tacrolimus metabolism. Body composition shifts with age from less lean to more fat tissue, which can alter the distribution profile of tacrolimus [46]. Tacrolimus is highly lipophilic, so there is a tendency for higher tissue accumulation with a higher percentage of body fat. Additionally, tacrolimus binds extensively to red blood cells, so changes in the blood composition profile can also impact circulating levels of tacrolimus. Changes in the expression and activity of P-gp transporters (ABCB1) with age may impact the levels of tacrolimus that reach the brain, and the risk for neurotoxicity [47].

Next-generation forms of tacrolimus have been developed to mitigate some of the pharmacokinetic variability of the original immediate release form [1]. These include an extended-release formulation and extended-release LCP-tacrolimus. Some studies show a reduction in pharmacokinetic variability with the extended-release formulation [48]. A meta-analysis of five studies (n=659) found that extended-release tacrolimus was associated with reduced risk for biopsy proven acute rejection at 12 months (RR 0.69, 95% CI 0.51 to 0.95; $p = 0.02$) [49], however, separate meta-analyses including 11 RCTs (n=2,678) found no significant differences in patient outcomes over four years [50]. LCP-tacrolimus uses MeltDose® technology which increases the bioavailability through slow drug release, leading to a

decrease in peak to trough concentration fluctuations [51]. Some studies have shown lower rejection rates with this formulation [52]. It is anticipated that this formulation will be associated with less long-term toxicity [1].

Drug interactions: According to [Drugs.com](https://www.drugs.com), 745 drugs are known to interact with tacrolimus, including 227 major interactions. Due to its immunosuppressive properties, live vaccines should not be administered while taking tacrolimus. Grapefruit may interfere with the metabolism of tacrolimus and should be avoided. Alcohol use should also be avoided. Tacrolimus increases the risk for sunburn, so direct sun exposure should be limited and sunscreen should be used while taking tacrolimus.

The FDA levels indicates drug interactions with mycophenolic acid products, nelfinavir and grapefruit juice, CYP3A inhibitors, and CYP3A4 inducers.

Sources and dosing:

Tacrolimus is available in an oral formulation as an immediate release formulation (Prograf®) manufactured by Astellas Pharma, but is also available as a generic. In adult kidney transplant patients, the recommended initial dose is 0.2 mg/kg/day when used with azathioprine (observed blood trough concentrations should range from 7-20 ng/mL [months 1-3] and from 5-15 ng/mL [months 4-12]), and at a dose of 0.1 mg/kg/day in combination with MMF (observed blood trough concentrations 4-11 ng/mL) ([FDA label](#)). In liver transplant patients the dose is 0.10-0.15 mg/kg/day (5-20 ng/mL) for adults and 0.15-0.20 mg/kg/day (5-20 ng/mL) for children. In adult heart transplant patients, the dose is 0.075 mg/kg/day (10-20 mg/mL months 1-2; 5-15 ng/mL months 4-12). It is administered in the form of oral capsules (0.5 mg, 1 mg and 5 mg), or via injection (5 mg/mL i.v.). It is usually administered twice a day, and if the dosages are unequal, the larger dose should be taken in the evening due to difference in metabolism throughout the day.

ASTAGRAF XL® is the extended-release formulation from Astellas Pharma. It is administered as oral capsules (0.5 mg, 1 mg, 5 mg) and should be taken at the same time every morning on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal ([FDA label](#)) The target blood trough concentrations are 7 to 15 ng/mL (with basiliximab induction) 10 to 15 ng/mL (without basiliximab induction) for the first month then, 5 to 15 ng/mL for months 2-6.5 then 5 to 10 ng/mL, after 6 months.

ENVARUSUS XR® is the extended-release LCP-tacrolimus formulation from Veloxis Pharmaceuticals. It is taken once per day as oral capsules (0.75 mg, 1 mg, 4 mg), at the same time each day, preferably in the morning on an empty stomach ([FDA label](#)). The recommended dose is 0.14 mg/kg/day (blood trough



concentration 4-11 ng/mL). An observational study found that the current recommended dose may be too high, and that blood trough concentrations in the 7-10 ng/mL range could be achieved with doses of 0.064 mg/kg [51].

It is important to note that these different formulations are not bioequivalent, and frequent drug concentration monitoring is needed when switching between formulations.

The topical formulation of tacrolimus (PROTOPIC®) from Astellas Pharma is available in concentrations of 0.03% and 0.1% for adults, and 0.03% for children aged 2 to 15 years ([FDA label](#)). It should only be applied to affected areas for short-term or non-continuous chronic use.

Research underway:

According to [Clinicaltrials.gov](#), there are currently 349 active clinical trials for tacrolimus. The trials are primarily related to its use in organ transplant.

Search terms:

Pubmed, Google: Tacrolimus

- Alzheimer's disease, Parkinson's disease, stroke, aging, cardiovascular, diabetes, safety, meta-analysis, systematic review, toxicity

Websites visited for Tacrolimus:

- [Clinicaltrials.gov](#)
- [Drugs.com](#)
- [WebMD.com](#)
- [PubChem](#)
- [DrugBank.ca](#)
- [Cafepharma](#)

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