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REVIEW ARTICLES OF TOPICS

Tacrolimus (FK506): Safety and Applications in Reconstructive Surgery

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Abstract Tacrolimus (FK506) is a macrolide immunosuppressive drug that is approved for the prevention of allograft rejection. It is a standard component of immunosuppressive regimens currently in use for organ and reconstructive tissue transplants. The experimental literature has demonstrated potential efficacy in the management of other diseases for which transplantation does not play a role. The ability of tacrolimus to modulate the immune system and inhibit T cell activation provides a potential benefit for the treatment of disorders in which autoimmune phenomena are central to their pathogenesis such as rheumatoid arthritis and inflammatory bowel disease. Tacrolimus also has well-established neuroprotective and neuroregenerative properties through both similar and different mechanisms that have been extensively demonstrated in both small and large animal models. However, as a potent immunosuppressive agent, it can cause serious adverse effects, some of which are irreversible and potentially life threatening. This article reviews its safety under different therapeutic requirements and applications in both allogeneic and autogenous tissue reconstruction.

Keywords Tacrolimus · FK506 · Transplantation · Nerve · Nerve regeneration · Rheumatoid arthritis · Nerve injury · Safety · Adverse effects · Clinical trials

Introduction

Tacrolimus (Prograf, FK506) is a hydrophobic macrolide isolated from *Streptomyces tsukabaenis* and has well-established immunomodulatory and anti-inflammatory properties. It is approved for the prophylaxis of transplant allograft rejection and primarily affects T cell function by binding to FK binding proteins (FKBP), and mediates immunosuppression by inhibiting calcineurin, a calcium- and calmodulin-dependent phosphatase. The primary biologic effect of calcineurin inhibition includes the decreased production of inflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin-2, and interferon-γ. As such, it is an effective inhibitor of human T cell proliferation with a potency ~100-fold greater than cyclosporine A. It is extensively metabolized by demethylation and hydroxylation mainly by the cytochrome P450 system [19, 80]. The receptors for FK506 belong to the family of FKBPs, and are designated according to their molecular weight [5]. The drug's immunosuppressive affects are mediated largely through FKBP12 which is involved in intracellular calcium flux and cell cycle regulation [82]. However, its neuroregenerative effect is also related to its receptor FKBP52, a heat-shock protein (HSP-59) and a component of mature steroid receptor complexes, as well as FKBP 12 [31]. Therefore, the potential exists to optimize the neurologic effect independently of the immunosuppressive properties either through dose modification, or ultimately through pharmacologic modification of drug structure.

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Experimental Literature

Enhancement of Nerve and Muscle Recovery

In the experimental literature, tacrolimus has been shown to have numerous neuroprotective and neuroregenerative effects in multiple of models of nerve injury [78, 91],

including models of (1) spinal cord trauma [8, 32, 57, 84, 93], (2) Parkinson's disease [18, 25, 30, 37, 38], (3) nerve crush [33, 34, 94, 99], and (4) nerve transection [3, 4, 21]. Its neuroregenerative effects upon binding to FKBP-12 include (1) activating growth associated protein-43 (GAP-43) via the inhibition of the phosphatase activity of calcineurin, (2) stimulation of the TGF-β_1 pathway [26], and (3) enhancing Schwann cell proliferation [11, 26]. Its effects associated with FKBP-52 binding include (1) increasing the expression of c-jun and GAP-43, (2) stimulating the MAP kinase pathway, and (3) interacting with cytoskeletal components [30, 32]. The benefits of tacrolimus therapy after peripheral nerve injury has been shown to include (1) faster onset of functional recovery, (2) enhancing regeneration in rodent models of axonotmetic [33, 54] and neurotmetic injury [21, 68], (3) reducing the time period of denervation and its associated negative effects (muscle atrophy and loss of motor endplates), and (4) accelerating collateral axonal sprouting [90].

The acceleration of nerve regeneration has been quantified in rodent models of neurotmetic and crush injury as assessed by histomorphometric and functional outcomes [21, 54]. In the rat model of crush injury to the posterior tibial nerve, treatment with tacrolimus showed significantly faster recovery of hindlimb function by 14 days post-injury as compared to 18 days with cyclosporine A (CsA) treatment and 20 days for untreated controls. The rat models of posterior tibial nerve transection and repair or nerve graft reconstruction of a 2-cm nerve gap further verified the enhancement of nerve regeneration with tacrolimus. After transection and repair, a much higher degree of axonal regeneration was seen 4 weeks post-injury as compared to CsA and untreated controls. CsA was also shown to increase the rate of nerve regeneration but not to the same degree as FK506 and is not quite as effective as an immunosuppressant [50]. The nerve graft model showed greater nerve regeneration with use of a calcineurin inhibitor (CsA, tacrolimus) by multiple histomorphometric parameters including total axon number and percent neural tissue as well as the regeneration of a significantly greater percentage of large myelinated fibers >3.0 μm compared to control animals. Tacrolimus has also been shown to double the number of axons that regenerate following a nerve injury, increase the number of myelinated axons by 40%, and significantly increase myelin thickness in a model of chronic axotomy [85]. In addition, tacrolimus reduces by half the time to neurological recovery following a nerve lesion, and also enhances collateral sprouting of peripheral nerve fibers [92]. Other documented effects have also included increasing the caliber of regenerating axons and the rate with which they are remyelinated [54, 94]. Tacrolimus has also been shown to ameliorate other factors that may inhibit nerve regeneration and counteract the effect of agents that are detrimental to functional recovery after peripheral nerve injury [73]. These results have been confirmed in numerous *in vitro* and *in vivo* studies [9, 14, 15, 27, 29, 32, 65]. In the setting of nerve and hand transplantation, and in the only reported case of its use after replantation of an upper arm, improvement in nerve regeneration and recovery has been noted with tacrolimus therapy [22–24, 49, 55, 59–61, 74].

Because the neuroregenerative and immunosuppressive effects appear to act through different mechanisms, a low sub-immunosuppressive dose of tacrolimus that can still speed the rate of nerve regeneration without inducing immunosuppression has been demonstrated. In the rat model, doses of tacrolimus sufficient to permit survival of skin allografts with full major histocompatibility complex disparity also accelerated nerve regeneration after nerve injury and repair. Further decreases in the dosage of treatment by 50% and 75% were no longer sufficient to prevent rejection of the skin allograft, but still demonstrated enhancement of neuroregeneration [98].

Clinical Literature

Adverse Effects of Tacrolimus

The primary morbidity of tacrolimus stems from the lifelong general immunosuppression that is required for the survival of transplanted organs and tissues. As organ allografts are generally vital and because reconstructive allografts involve multiple heterogeneous tissue types, some of which are highly antigenic, not only must immunosuppression be chronic but it must be maintained at relatively high therapeutic levels. When the complications are considered collectively, lifelong immunosuppression can be considered a chronic disease characterized by its own set of risks. Much as chronic hypertension increases one's risk of stroke or heart attack, permanent immunosuppression increases the risk of infection, fracture, neoplasia, drug toxicity including hypertension and nephrotoxicity, and metabolic derangement such as hyperlipidemia and diabetes mellitus [12]. Infections account for a major part of the post-operative morbidity in solid organ transplants. The etiology may be bacterial, viral (CMV, HSV, VZV), or fungal, and their prevalence varies with the type of transplant and the degree of immunosuppression [81]. The nephrotoxicity of immunosuppressants has also been well studied and is potentially the most serious side effect. Factors that contribute to hypertension include altered renal vascular reactivity and vasoconstriction, increased sympathetic tone, and sodium retention [76]. The metabolic derangements seen in the setting of chronic immunosuppression take a variety of forms. Among the best studied of

these are increased risk of fracture due to loss of bone density [13, 41] and increased prevalence of hyperlipidemia and diabetes [19, 95, 97, 104] with the specific abnormalities depending on the immunosuppressive regimen selected. Recipients of organ transplants also have a significantly increased risk of developing cancer. The most common malignancies seen in transplant recipients are skin cancers, which account for 36% of post-transplant tumors. The incidence varies with the type of transplant, geographical location, and sun exposure [53, 72, 75]. Post-transplant lymphoproliferative disorders (PTLD) are the second most common malignancies after transplantation with an incidence between 1% and 32% depending on the type of allograft [77]. As such, the clinical application of tacrolimus solely for its neurologic properties has never been studied. But the adverse sequelae of immunosuppression is a cumulative result of its long-term use and most of the current literature is based on organ transplant recipients who require lifelong treatment with high doses of immunosuppressive multiple-drug therapy to prevent allograft rejection.

The controversy over the application of tacrolimus for non-vital reconstructive purposes where the primary focus is the restoration of function and form rather than the treatment of a life-threatening condition centers on patient safety given its serious side effects. The benefits of hand and face transplantation have now been demonstrated more clearly and these procedures are slowly gaining acceptance. The application of tacrolimus for indications other than transplantation such as peripheral nerve injuries for its neuroregenerative effect requires a closer analysis of its potential benefit and its safety when prescribed under different conditions of duration and dosage level. In support of broadening its application, a growing literature base exists on the temporary use of tacrolimus for reconstructive allografts that are ultimately incorporated by host tissue, and its more recent application for diseases whose treatment do not require transplantation. The latter application especially to date includes multiple phase II and III clinical trials, dose-ranging studies, and several smaller open-label trials, which collectively have helped to define the actual incidence of adverse events when used in a more elective manner based on a lower range of pharmacologic dosing and a much more limited timeframe.

Temporary Tacrolimus Therapy in Reconstructive Transplantation

In most cases, clinical transplantation requires lifelong immunosuppression to prevent the rejection of permanent vital organ transplants or reconstructive tissue allografts such as the hand or face. However, there have been several reported series of reconstructive tissue transplants which act as a ‘scaffold’ for the ingrowth of host tissue and for which immunosuppression can be stopped once regeneration and incorporation of the transplant is completed. Mackinnon has reported a series of nerve transplants for the reconstruction of severe nerve injuries with long segmental gaps of major peripheral nerves and demonstrated no morbidity from the temporary use of tacrolimus [55, 56]. This application requires immunosuppression only until the host nerve has regenerated through the nerve allograft to reinnervate the target muscles whose functions are critical and targeted for reinnervation. No induction therapy was used and the treatment regimen included either CsA or tacrolimus, azathioprine, and prednisone at standard therapeutic doses for approximately 1.5–2 years, rather than lifelong treatment that is necessary for organ allografts. In the only reported case of tacrolimus therapy after upper arm replantation, the authors noted “exceptional” results with clinical and electromyographic evidence of reinnervation of intrinsic hand muscles [61]. Adverse sequelae related to standard maintenance doses of general immunosuppressive medications were not seen when used for a relatively short time period. There has also been a small series of allogeneic vascularized human femoral diaphyses and total knee joint transplants reported in 1998 [42, 43]. Immunosuppression began with quadruple-drug induction therapy with CsA, azathioprine, anti-T-lymphocyte globuline (ALG), and methylprednisolone, followed by oral maintenance therapy with CsA and azathioprine which were stopped after 2 years in recipients of femoral diaphyseal allografts, but was indefinite for the knee joint allografts. With follow-up of at least 2 years, no adverse effects related to the immunosuppression were reported for either type of allogaft nor was there any interference with bony healing. In 1992, two cases of human vascularized digital flexor tendon and pulley system transplantation were reported [36]. CsA immunosuppression was discontinued after 6 months during which renal, cardiac, and hepatic function was monitored and noted to be stable and unchanged. Satisfactory healing and successful recovery of function were achieved in both cases. Although small in numbers, in general, these series support the safety of the short-term and monitored use of standard maintenance immunosuppressive therapy, especially when employed as single-drug monotherapy. But even as multiple-drug therapy, adverse effects have been temporary and readily responsive to appropriate modification of dosage and drug therapy [83].

Clinical Application of Tacrolimus in Non-transplant Patients

To date, there is a substantial and accumulating literature base on the use of tacrolimus for diseases that do not involve transplantation. The most extensive and informative data come from its application for the treatment of

rheumatoid arthritis (RA). Since 2002, there have been two phase II clinical trials (USA and Japan), one phase III clinical trial (USA), at least two open-label studies (USA and Japan), and other small and large series (n>200) evaluating efficacy compared to or in combination with other disease modifying anti-rheumatic drugs [2, 20, 28, 51, 52, 64, 67, 86, 100–102]. Other systemic applications have also included the treatment of myasthenia gravis, ulcerative colitis, Crohn's disease, juvenile dermatomyositis, systemic lupus erythematosus, and ocular disease [6, 16, 35, 39, 40, 44, 48, 66, 71, 79, 87, 88, 96, 103]. Collectively, these have involved study enrollment in the range of 2,000 patients or more for indications other than transplantation and have included reports focused on the correlation of drug safety with pharmacologic dosing.

The first dose-ranging study (2002) was a phase II, randomized, double-blind, placebo-controlled monotherapy study which enrolled 268 patients over a 6-month study period and evaluated tacrolimus at 1 mg, 3 mg, or 5 mg/day vs. placebo [28]. In the placebo group, adverse effects that did not require any change in dosage or therapy occurred in 75%, which is consistent with other studies even for patients not receiving any drug treatment. Similar side effects were seen in 89–93% of the tacrolimus groups. The most common adverse events were gastrointestinal (GI) including nausea and diarrhea, neurologic (headache, tremor), respiratory, musculoskeletal, and urologic (urinary tract infection (UTI), dysuria). Although no clear dose response was apparent, some side effects were clearly associated with a particular dosage such as diarrhea, tremor, and anxiety in the 5 mg group, and nausea and UTI in the 3 mg group. Treatment discontinuation was mostly due to gastrointestinal side effects and occurred in 8.5% of the placebo group and 7.2%, 15.6%, and 12.5% in the 1 mg, 3 mg, and 5 mg groups, respectively. Renal function was closely monitored and 40% increases in serum creatinine levels above baseline were seen in 7%, 9%, 19%, and 28% of patients in the placebo, 1 mg, 3 mg, and 5 mg groups, respectively, at some point. With treatment continuation, normalization to baseline levels occurred in 100% of the placebo and 1 mg groups, and 83% and 61% of the 3 mg and 5 mg groups, respectively. In most cases, creatinine bumps were only transient despite continued therapy. In all patients who discontinued treatment, the creatinine levels normalized within 4 weeks of stopping medication. The number of patients who discontinued therapy due to nephrotoxicity was very small, only two in the 3 mg group and none in the 1 mg group. There were no infectious or neoplastic complications.

The second dose-finding study (2004) was also a randomized, double-blind, placebo-controlled study that enrolled 212 patients but also allowed continuation of prednisolone (≤5 mg/day) and/or one non-steroidal anti-inflammatory drug (NSAID) during the study period of at least 6 months [52]. Placebo was compared to tacrolimus at 1.5 mg and 3 mg/day. Adverse events were similar, occurring in 46.3%, 61.3%, and 44.4% in the placebo, 1.5 mg, and 3 mg groups, respectively, and were not statistically significant either individually or in total. Again, the most frequent side effects were gastrointestinal, occurring in 9%, 4.8%, and 11.1% in placebo, 1.5 mg, and 3 mg, respectively, and renal function abnormalities. Elevation in serum creatinine ≥0.3 mg/dl (or ≥0.2 if baseline was ≤0.5 mg/dl) was seen in 0%, 3.3%, and 16.1% in the placebo, 1.5 mg, and 3 mg groups, respectively. Glucose tolerance abnormality (fasting blood sugar ≥110 mg/dl or blood sugar ≥160 mg/dl) was noted in 41.1%, 16.7%, and 19.2% in the placebo, 1.5 mg, and 3 mg groups, respectively. Infections occurred in 13.4%, 4.8%, and 0% in the placebo, 1.5 mg, and 3 mg groups, respectively. Those in the 1.5 mg group included pharyngitis, upper respiratory infection, and common cold, but in each case a relationship with tacrolimus use was ruled out. Four serious adverse events occurred and consisted of fever, vomiting, and staphylococcal sepsis in two patients (3%) in the placebo group, and uterine fibromyoma in one patient (1.6%) in the 1.5 mg group. The patient with uterine fibromyoma had already developed a hysteromyoma so a causal relationship with the study drug was ruled out, leaving no drug-related serious adverse events in either tacrolimus group. Treatment discontinuation occurred in 40.5%, 26.5%, and 22.9% in the placebo, 1.5 mg, and 3 mg groups, respectively, and was due to inefficacy or adverse effects.

The largest patient-safety study was an open-label study undertaken to determine the long-term safety of tacrolimus monotherapy for the treatment of RA (2004) [100]. A total of 651 patients received tacrolimus 3 mg/day for ≥6 months; 497 were treated ≥12 months and 54 received 18 months of treatment. The median trough tacrolimus levels were 2–3 ng/ml and the level did not accumulate over the course of the study. The incidence of adverse events previously identified as safety concerns in transplant studies were in general notably lower in the study patients that received 3 mg/day for up to 18 months than transplant patients, including hypertension (9.2% vs. 38–50%), tremor (10.5% vs. 48–56%), diabetes (<5% vs. 24%), and increased creatinine (7.4% vs. 24–45%) [1]. Furthermore, multiple other side effects such as insomnia, paresthesias, oliguria, hyper or hypokalemia, hyperglycemia, hypomagnesemia, hypophosphatemia, anemia, and peripheral edema that have a reported incidence of at least 15% in liver and/or kidney transplant patients occurred in less than 5% of patients in this study. This has been attributed to the lower dose used to treat rheumatoid arthritis (3 mg/day) as compared to the prevention of transplant rejection (0.1–0.2 mg/kg/day). In

addition, no increase but an actual decrease in the initial incidence of adverse effects was seen with longer duration of treatment in RA patients.

A final retrospective study focused on the safety profile of tacrolimus as used in a previous randomized double-blind controlled study (2008) [2]. The findings were similar to the previous safety studies with GI symptoms being the most common and significant adverse reaction which was the main reason for discontinuation of therapy. The mechanism(s) involved in the occurrence of GI symptoms is not completely clear but tacrolimus has been noted to increase gastrointestinal motility in animal models [17]. In the clinical literature, it has been shown to increase the gastric emptying rate in kidney transplant recipients and cause gastrointestinal symptoms with a higher frequency than CsA [58, 62, 63, 89]. Tacrolimus has the same macrolide structure as erythromycin which has been shown to have similar gastrointestinal effects experimentally, and both may act by mimicking the effect of motilin [45–47]. This study demonstrated that the frequency of GI symptoms was significantly higher when a dose of ≥2 mg/day was used compared those receiving <2 mg/day.

The general consensus collectively reached based on these trials has been that tacrolimus is effective and will play a role in the treatment of RA through its effect on T cell activation, which has been established to be central to the pathogenesis of RA, and that it is safe and generally well tolerated with a low incidence of serious or irreversible adverse events. The literature on its application to the management of severe and refractory ulcerative colitis and Crohn's disease has led to similar conclusions regarding safety and efficacy but is less definitive based on much smaller patient numbers and the relative lack of randomized controlled trials [6, 7, 10, 69, 70, 105]. However, initial trials have shown promise for the improvement of symptoms and the prevention of colectomy in the short term. Taken together, the collective opinion has been consistent, that further trials are warranted, do not place patients at prohibitive risk, and should be forthcoming.

Summary

There is accumulating literature that supports the notion that the morbidity of a limited course of appropriately monitored monotherapy with tacrolimus at low maintenance doses is acceptably low, reversible, and safe, and that it is the cumulative effect over years and decades of high-dose multiple-drug immunotherapy that leads to the serious and irreversible complications seen in the organ transplant literature. Tacrolimus appears to have more to offer in the management of autoimmune diseases. Potential application to the treatment of nerve disorders and injury remains speculative but compelling. It is clear that the use of tacrolimus in the clinical setting requires a high level of caution and careful consideration of risks vs. potential benefits in addition to close follow-up and monitoring for adverse sequelae. Future trials need to be optimally designed with a high degree of scientific rigor for statistical validation and should use validated disease activity and outcome scores including quality of life assessment to permit definitive conclusions as broader applications are defined.

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