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Tacrolimus for the treatment of rheumatoid arthritis: are broad-based immunosuppressants still valid?

Benjamin D Schwartz[†]
& Laurel J Mengle-Gaw

[†]*Author for correspondence*
The Camden Group, 19 Oak Park Drive, St. Louis, MO 63141, USA
Tel.: +1 314 220 7067;
Fax: +1 314 432 5066;
camden@camdengroup.com

Tacrolimus is an immunosuppressive drug that is approved and currently used primarily for the prophylaxis of liver, heart and kidney allograft rejection. Recently, oral tacrolimus 1.5–3 mg/day has been approved in Japan and Canada for the treatment of rheumatoid arthritis in patients who respond insufficiently to other therapies. Tacrolimus potently inhibits calcineurin and, consequently, T-cell activation and proliferation with a mechanism similar to that of cyclosporine. Clinical studies of the efficacy and safety of tacrolimus as monotherapy and in combination with methotrexate have shown it to be less effective than many of the biologics, but similar to cyclosporine for symptomatic relief. Unlike the biologics and other immunosuppressants, it has not been shown to retard progression of joint damage on x-ray. However, clinical response, when it does occur, can be robust and appears to be maintained for at least 18 months. Longer-term safety and efficacy in rheumatoid arthritis have not been studied. In addition, tacrolimus is relatively inexpensive and its oral formulation makes it convenient for the patient to use. The available data suggest that tacrolimus may be a useful alternative to other broad immunosuppressants and biologics in patients who are refractory to, or intolerant of, these other drugs.

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Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by symmetric, erosive synovitis and irreversible cartilage and joint destruction. It has a prevalence of approximately 1% worldwide [1]. Early diagnosis and aggressive treatment are required to minimize the morbidity associated with its progression. Until relatively recently, the poorly understood nature of the disease dictated treatment with a pharmacopoeia of broad-based anti-inflammatory and immunosuppressant drugs that were titrated in creative fashion, alone and in combination, with often less than stellar clinical results and dose-limiting side effects. These drugs included corticosteroids, gold, methotrexate (MTX), leflunomide, sulfasalazine, hydroxycloroquine and cyclosporine. MTX demonstrated the most therapeutic promise, both as monotherapy and in combination with other drugs, and became the gold standard for disease-modifying therapy for RA. The recent recognition of the dominant role played by T-cell mediated immune processes in the pathogenesis of the disease has led to the development of targeted therapies that have significantly enhanced the clinical outcome and long-term prognosis for many patients. In particular, the introduction of tumor necrosis factor (TNF)-antagonists, interleukin (IL)-1-antagonists, B-cell targeted therapies and costimulation blockers have shown great therapeutic promise and have widened the spectrum of pharmacological alternatives for physicians and their patients. The goal of RA treatment is to successfully walk the tightrope between clinical response and toxicity.

The advent of biologics has not eliminated the need for polypharmacy, and these drugs more often than not are being combined with one or more broad-based immunosuppressants and occasionally with each other to optimize effect. Indeed, the combination of etanercept and MTX has been shown to be more efficacious than either agent alone [2]. Furthermore, the manufacturing complexity of these biological therapies is reflected in higher cost to the patient and to society. Like the broad-based therapies, biologics do not work for all patients and some patients can become refractory to their effects with long-term use. The biologics are also associated with drug- and class-specific safety risks and are not suitable for all patients. The realization that the biologics do not constitute a cure-all suggests there is still an unmet medical need in the treatment of RA. Tacrolimus, a relatively broad-based immunosuppressant, has been studied for the treatment of RA. The subject of this review is to evaluate the place of tacrolimus on the prescription pad of rheumatologists, in the age of targeted biologic therapies for RA.

Tacrolimus: a macrolide calcineurin inhibitor

Tacrolimus (Prograf®, FK506; empirical formula $C_{44}H_{69}NO_{12}\cdot H_2O$) is an immunosuppressive macrolide isolated from the fermentation broth

of *Streptomyces tsukubaensis*. Tacrolimus potently inhibits antigen-specific T-cell activation and proliferation through a mechanism that has been only partly elucidated. Tacrolimus binds to a T-cell cytoplasmic protein, FK-506 binding protein, and the tacrolimus-FK-506 binding protein complex inhibits calcineurin, a calcium- and calmodulin-dependent phosphatase that is required for the activation of the nuclear factor of activated T cells (NF-AT), which is, in turn, required for the expression of cytokine genes in T cells. Immunosuppressive consequences of calcineurin inhibition include decreased antigen-stimulated IL-2 T-cell production and decreased transcription of early activation genes for cytokines, such as IL-2, interferon (IFN)-γ and TNFα; inhibition of IL-2 synthesis and release; and decreased IL-2 receptor expression on activated T cells [3–7]. Although the mechanism of action of tacrolimus is similar to that of cyclosporine, a calcineurin inhibitor that has been approved in the USA for the treatment of RA, its immunosuppressive potency is 30- to 100-fold greater *in vitro*, and 10- to 20-fold greater *in vivo*, than that of cyclosporine [8].

Pharmacodynamic properties relevant to rheumatoid arthritis

Tacrolimus suppresses T-cell activation and blocks production of T-cell derived inflammatory cytokines [9]. *In vitro* studies have shown that tacrolimus inhibits the production of TNFα, IL-1β and IL-6 from T-cell activated human peripheral blood mononuclear cells (PBMCs) without affecting cytokine production or proliferation of normal bone marrow hematopoietic progenitor cells [10,11]. Tacrolimus inhibits TNFα and IL-1β in human PBMCs at lower concentrations and with less cytotoxicity than either cyclosporine or dexamethasone [10].

Tacrolimus inhibits activated T-cell-driven production of inflammatory cytokines *in vivo* in animal models of arthritis [12–14] and *ex vivo* in isolated synoviocytes [15]. Levels of TNFα, IL-1β and IL-6 were reduced by tacrolimus in joint tissue from rats with adjuvant- and collagen-induced arthritis, and in serum and joint tissue from animals with peptidoglycan polysaccharide-induced polyarthritis. IL-6 expression was reduced by tacrolimus in isolated human rheumatoid synoviocytes [15].

In vivo studies in animal models have also shown that tacrolimus suppressed inflammation, reduced cartilage and bone damage, and improved joint function in animals with established adjuvant-, collagen- and peptidoglycan polysaccharide-induced arthritis [13,14,16,17], and prevented development of collagen- and adjuvant-induced arthritis [12,18]. Tacrolimus was shown to be more effective and less toxic than MTX or leflunomide in established adjuvant arthritis [17]. Tacrolimus has also been shown to effectively reduce hyperalgesia in inflamed paws of rats with adjuvant-induced arthritis, concomitant with a reduction of paw IL-1β levels; cyclosporine treatment has a similar effect [19].

Tacrolimus may exert protective effects on bone and cartilage via a calcineurin-independent mechanism [9]. Tacrolimus has been shown to stimulate osteogenic, chondrogenic and osteoblastic differentiation in *in vitro* studies [20,21], and to increase bone formation in *in vivo* studies in rats [22].

Pharmacokinetics & metabolism

Administration of a single 3 mg dose of tacrolimus in RA patients resulted in a mean peak whole-blood concentration (C_{max}) of 19.64 ng/ml after 1.3 h (T_{max}) with a mean area under the whole-blood concentration-time curve (AUC) of 192.88 ng × h/ml [101]. Absorption is greatest in the fasted state. A high fat meal decreased the mean AUC and C_{max} by 37 and 77%, respectively in RA patients, and T_{max} was increased fivefold in healthy volunteers [101,102]. Multiple-dose administration of once-daily tacrolimus 3 mg to RA patients, either alone or with concomitant MTX administration, resulted in median trough whole-blood concentrations of 2–3 ng/ml, with no accumulation [23,24]. The absolute bioavailability of tacrolimus is reported to be approximately 25% in adult RA patients [101].

Tacrolimus is highly bound to erythrocytes, and uptake is drug concentration dependent. In plasma, it is approximately 99% bound to plasma proteins, primarily albumin and α-1-acid glycoprotein. Partitioning of tacrolimus between whole-blood and plasma is affected by hematocrit, temperature at the time of plasma separation, drug concentration and plasma protein concentration [101,102]. The apparent volume of distribution of tacrolimus in adult RA patients is 2.37 l/kg, based on whole-blood concentrations [101].

Tacrolimus is metabolized in the liver and intestinal wall by cytochrome P450 CYP3A4, with less than 1% of the unchanged drug excreted in urine [101,102]. Biliary excretion is the principal route of excretion, with 93% of an orally administered ^{14}C-labeled tacrolimus dose

recovered in the feces [25]. The terminal elimination half-life of oral tacrolimus in RA patients is 35.2 h, thereby permitting once-daily dosing [101]. Multiple metabolites have been identified, but only one metabolite, 13-demethyl tacrolimus, shows significant immunosuppressive activity *in vitro* [25,101,102].

Co-administered drugs which are metabolized by the CYP3A4 metabolic pathway may affect the pharmacokinetics of tacrolimus [25,101,102]. In particular, certain calcium channel blockers, antifungal agents, macrolide antibiotics, and gastrointestinal prokinetic agents which inhibit CYP3A4 may increase tacrolimus concentrations, while anticonvulsants, antimicrobials and herbal preparations that induce CYP3A4 may decrease tacrolimus concentrations. Clinical studies in healthy volunteers have shown a significant increase in tacrolimus oral bioavailability with concomitant ketoconazole administration, increased mean tacrolimus AUC with concomitant magnesium–aluminium–hydroxide administration, and decreased tacrolimus oral bioavailablity with concomitant rifampin administration [101]. Tacrolimus has been shown to significantly reduce the metabolism of cyclosporine [101]. A repeated-dose study in RA patients receiving a stable dose of MTX along with tacrolimus 3 mg/day showed no pharmacokinetic interactions between tacrolimus and MTX [26]. This lack of interaction is in contrast to the observed increase in MTX plasma levels when RA patients are treated with MTX plus cyclosporine [27].

Clinical experience with tacrolimus in adult RA

Monotherapy

Once-daily oral tacrolimus has been studied both as monotherapy in patients with active RA resistant to, or intolerant of, disease-modifying antirheumatic drugs (DMARDs) [23,28–31] and in combination with MTX in patients with active disease despite stable MTX therapy [24,103]. Tacrolimus was administered as monotherapy in one open-label pilot study [28], three double-blind, placebo-controlled, multi-center trials of 4–6 months duration [29–31], and in one 12-month open-label study [23]. Efficacy was assessed according to the combined response criteria of the American College of Rheumatology (ACR) [32]. A summary of the results are shown in Table 1.

Results from an open-label pilot study in which 12 patients with severe or refractory RA were treated with tacrolimus 2–6 mg/day showed that all seven patients who completed the 6-month treatment period achieved a 20% improvement from baseline in the response criteria of the ACR

Table 1. Efficacy of tacrolimus in rheumatoid arthritis patients.

Study	ACR20 (%)	ACR50 (%)	ACR70 (%)	Median improvement in swollen joint count (%)	Median improvement in painful joint count (%)
Phase II dose ranging (6-Mo; DB) [29]					
Placebo	15.5	1.4	NR	NR	NR
1 mg	29.0	14.5*	NR	NR	NR
3 mg	34.4*	17.2*	NR	NR	NR
5 mg	50.0*	14.1*	NR	NR	NR
Phase III (6-Mo; DB) [31]					
Placebo	13.4	4.5	0.6	5.9	2.2
2 mg	21.4	11.7*	5.2*	16.7*	10.5
3 mg	32.0*	11.8*	3.3	30.0*	30.0*
Phase III (12-Mo; OL) [23]					
3 mg	38.4	18.6	9.0	NR	NR
Phase III (6-Mo; OL) [24]					
3 mg + MTX	52.5	28.8	13.8	NR	NR
Phase III (6-Mo; DB) [103]					
Placebo + MTX	28.4	9.0	4.5	15.1	36.9
3 mg + MTX	40.8	15.0	4.1	46.3*	51.7*

**Statistically significantly different from placebo.*

6-Mo: 6 month trial; 12-Mo: 12-month trial; ACR: American College of Rheumatology; DB: Double-blind trial; OL: Open-label trial; MTX: Methotrexate; NR: Not reported.

(ACR20), and five of the seven patients achieved an ACR50 [28]. The five patients who withdrew from the study did so within the first 3 months of treatment, owing to gastrointestinal symptoms (three patients), chest pain and neuropathic pain (one patient each). No changes in serum creatinine levels were observed, nor were there any reports of treatment-emergent hypertension in any of the patients.

Phase II dose-finding studies evaluated tacrolimus monotherapy in patients who had failed MTX [29] or other DMARDs [30]. A randomized, placebo-controlled study was performed in 268 patients who had failed MTX (defined as intolerance of or resistance to MTX therapy) and who were treated with a once-daily dose of oral tacrolimus 1, 3 or 5 mg/day for 6 months [29]. Patients discontinued all DMARDs, including MTX, at least 4 weeks prior to the screening visit, and were required to have stable, active disease at both screening and baseline visits. At the end of treatment, the ACR20 responses were 15.5, 29.0, 34.4 and 50.0% in the placebo, 1, 3 and 5 mg groups, respectively. ACR50 response rates were 1.4, 14.5, 17.2 and 14.1%, respectively. The differences in the ACR20 response rates for the tacrolimus 3 and 5 mg groups compared with placebo, and in the ACR50 response rates for the 1, 3 and 5 mg groups compared with placebo, reached statistical significance. Although the 5 mg dose was more effective than the other regimens, it was more nephrotoxic (as measured by an increased incidence of elevations in serum creatinine), and was associated with a significantly higher incidence of anxiety and tremor, and therefore was not tested in subsequent studies. A second double-blind, placebo-controlled dose-finding study was conducted in Japan,and involved 212 patients with active RA despite DMARD treatment [30]. Patients were excluded from the study if they had renal insufficiency or were taking more than one nonsteroidal anti-inflammatory drug (NSAID). Patients switched from their DMARD to tacrolimus 1.5 or 3 mg/day, or placebo with no DMARD washout period, thus, potentially confounding the results. The ACR20 response rate after 4 months of therapy was significantly higher in the 3 mg/day group (48.3%) compared with the placebo group (14.1%). The incidence of serum creatinine elevation (defined as an increase of 0.3 mg/dl or greater above baseline, or 0.2 mg/dl or greater above baseline if the baseline value was 0.5 mg/dl or less) was significantly higher in the tacrolimus 3 mg group (16.1%), compared with the 1.5 mg (3.3%) or placebo groups (0.0%). There was no increase in the incidence of infections with tacrolimus treatment, compared with placebo.

One Phase III, double-blind, placebo-controlled trial was conducted in 464 patients who had demonstrated either resistance to or intolerance of one or more DMARDs, had discontinued all DMARD therapy 4–12 weeks prior to study entry (dependent on the DMARD), and had stable, active disease at baseline [31]. Stable doses of concomitant NSAIDs and corticosteroids were allowed. Patients with renal insufficiency were excluded. Patients were randomized to receive placebo, tacrolimus 2 or 3 mg/day for 6 months. At the end of treatment, the ACR20 rates were 13.4, 21.4 and 32.0%, respectively; ACR50 rates were 4.5, 11.7 and 11.8%, respectively, and the ACR70 response rates were 0.6, 5.2 and 3.3%, respectively; for the placebo, 2 and 3 mg/day groups. At the end of treatment, patients receiving tacrolimus 2 mg/day had statistically significantly superior ACR50 and ACR70 response rates, compared with placebo, and patients receiving tacrolimus 3 mg/day had statistically significantly superior ACR20 and ACR50 response rates compared with placebo. Efficacy analyses were stratified by DMARD resistance (293 patients) versus intolerance (171 patients): DMARD-intolerant patients treated with either tacrolimus 2 or 3 mg had better ACR20, ACR50 and ACR70 response rates than did patients with a history of resistance to at least one previously administered DMARD, suggesting that clinical response to tacrolimus may be greater in patients who have not shown resistance to previous DMARDs. Of patients receiving tacrolimus, 13.3% withdrew early from the study due to adverse events. The most common adverse events occurring in patients receiving tacrolimus (≥7%, with ≥1% more than the incidence observed in patients receiving placebo) were diarrhea, abdominal pain, nausea, headache, asthenia, tremor and hypertension [101]. There was no difference in the overall incidence of adverse events in patients younger than 65 years of age, compared to patients older than 65 years. Serum creatinine levels increased by 30% or greater from baseline in 16.2, 25.5 and 33.7% of placebo, 2 and 3 mg/day patients, respectively, and by 40% or greater from baseline in 9.7, 20.1 and 29.1% of placebo, 2 and 3 mg/day patients, respectively. Hypertension was responsible for withdrawal of two patients

receiving 3 mg tacrolimus. Tremor was noted in 1.9, 4.5 and 8.5% of placebo, 2 and 3 mg/day patients, respectively.

Long-term safety and efficacy experience of tacrolimus 3 mg/day was collected in a 12-month open-label trial in 896 patients with active RA who had discontinued all DMARD therapy [23]. Some patients enrolled in this trial 'rolled over' from the 6-month double-blind trial [31], so the total exposure to tacrolimus 3 mg/day could have been up to 18 months; 19.8% of patients withdrew early from the study due to adverse events. For all common adverse events (i.e., incidence > 0.7%), there was at least one report of that adverse event within the first 3 months of treatment with tacrolimus 3 mg/day, suggesting that delayed appearance of any common adverse event is unlikely. Serum creatinine levels increased by 30% or greater from baseline in 40.3% of patients during the 12–18-month study period, with the majority of these patients (61.1%) returning to baseline levels with a mean time to return of 52.8 days. There was no indication that ACR response rates declined over time.

Combination therapy with methotrexate

Efficacy and safety of oral tacrolimus 3 mg/day in combination with oral MTX were studied in one open-label [24] and one double-blind trial [103]. In the open-label trial, 80 patients with active disease despite treatment with a stable, maximally tolerated dosage of oral MTX (≤20 mg/week) for 1 month or more prior to study entry and throughout the study received tacrolimus 3 mg/day for 6 months. ACR20, 50 and 70 response rates were 52.5, 28.8 and 13.8%, respectively, at end of treatment. The incidences of adverse events seen in this study were similar to the incidences observed in patients treated with tacrolimus monotherapy [101]. Serum creatinine levels increased by 30% or greater over baseline in 28.8% of patients during the study. Tacrolimus therapy was interrupted in some, but not all, patients with increased creatinine. While some patients' creatinine levels returned to baseline by the end of the study, it is unclear whether and to what extent return to baseline values was aided by interruption of dosing [24].

A 6-month double-blind trial with a 6-month open-label extension was performed in 214 patients with active RA, despite 3 or more months of treatment with MTX 10–25 mg/week [103]. Patients were randomized to receive tacrolimus 3 mg/day (147 patients) or placebo (67 patients) while continuing their stable dose of MTX. All other DMARDs were discontinued 4–8 weeks prior to the start of the study. Patients who completed the double-blind treatment period were eligible to enroll in the open-label extension, when all patients received tacrolimus 3 mg/day with stable MTX regimen. Efficacy was assessed primarily by ACR criteria, with x-ray progression at 6 and 12 months as planned exploratory endpoints. At the end of the double-blind phase, ACR20, ACR50 and ACR70 response rates were 40.8 versus 28.4%, 15.0 versus 9.0%, and 4.1 versus 4.5%, respectively, for the tacrolimus plus MTX versus placebo plus MTX groups. The differences were not statistically significant. For patients who received the study drug for 12 months and who had baseline and 12-month radiographs, smaller increases in erosion, joint space narrowing and total radiographic scores were observed in patients who received tacrolimus plus MTX for 12 months compared to patients who received placebo plus MTX for 6 months followed by tacrolimus plus MTX during the final 6 months of the study, suggesting that tacrolimus may contribute to retardation of joint destruction. However, the differences were not statistically significant. Similar results were observed for radiographic analyses at 6 months. Several retrospective subgroup analyses suggested that retardation of x-ray progression by tacrolimus may be greater in patients with aggressive, and erosive RA disease. Larger studies are needed to confirm this hypothesis. More patients receiving tacrolimus plus MTX (13.6%) withdrew from the double-blind portion of the study for adverse events, compared with patients receiving placebo plus MTX (4.5%) [103].

Comparison with other RA treatments

Tacrolimus has not been compared in head-to-head studies with other treatments for RA. A general comparison of the effects of tacrolimus with those of other RA agents can be made from a survey of the published literature (Table 2). The clinical efficacy and safety of tacrolimus more closely resemble cyclosporine than the biologics. Tacrolimus as monotherapy or in combination with MTX results in ACR20 responses of 30–40%, based on the results of controlled, double-blind trials. These response rates fall below those seen for most of the TNF-, T- and B-cell-targeted biologic therapies, alone and in combination with MTX (50–70%) as reported in published studies (Table 2). ACR50 and ACR70 response rates follow suit. Of the drugs with broader immunosuppressive action, leflunomide

Table 2. American College of Rheumatology response rates and disease-modifying antirheumatic drug effect of prescription rheumatoid arthritis drugs from published studies.

Treatment	ACR20 (%)	ACR50 (%)	ACR70 (%)	DMARD effect at 12 months
Tacrolimus (3 mg/day) [29,31]	32–34 (13–16)	12–17 (1–5)	3 (0.6)	NR
Tacrolimus (3 mg/day) + MTX [103]	41 (28)	15 (9)	4 (5)	NR*[103]
MTX [33]§	46 (26)	23 (8)	9 (4)	Yes [34]
Leflunomide [35]	55 (29)	33 (14)	10 (2)	Yes [34]
Cyclosporine [104]	25–35 (7–12)	NR	NR	NR
Cyclosporine + MTX [36]	48 (16)	NR	NR	Yes [37]
TNF antagonists [38,39]	46–65 (11–19)	22–40 (5–8)	12–21 (1–2)	Yes [40,41]
TNF antagonists + MTX [42–44]	50–71 (20–30)	27–39 (3–10)	8–21 (0–3)	Yes [2,45,46]
Rituximab + MTX [47]	54 (28)	34 (13)	20 (5)	Yes [105]
Abatacept [48]‡	53 (31)	16 (6)	6 (0)	NR
Abatacept + MTX [49,50]	68 (40)	40 (17)	20 (7)	Yes [50]
Anakinra [51]	43 (27)	19 (8)	1 (1)	Yes [52]
Anakinra + MTX [53]	38 (22)	17 (8)	6 (2)	NR

Data for ACR response rates are from double-blind, placebo-controlled trials, and are 6 months in length except where indicated. Where multiple trials have been performed with a particular agent, and/or where multiple agents within a category have been grouped together, ranges are given for the ACR response rates. Placebo response rates are given in parentheses and ranges are provided if appropriate. In trials where a drug is used in combination with MTX, the trial design had the drug added to ongoing MTX therapy; for these combination studies, placebo responses reflect responses to treatment with MTX plus placebo.

Data for DMARD effect are from 12-month double-blind trials where joint destruction has been evaluated radiographically.

**Direct comparison of radiographic results of tacrolimus + MTX vs placebo + MTX is only available from a 6-month trial.*

‡3-month trial.

§12-month trial for ACR response rates.

ACR: American College of Rheumatology; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; NR: Not reported.

treatment results in ACR20, 50 and 70 response rates higher than tacrolimus. Cyclosporine alone and in combination with MTX give similar ACR20 response rates to tacrolimus. Compared with MTX monotherapy, tacrolimus monotherapy gives lower ACR response rates. Furthermore, unlike the biologics and the other broad immunosuppressants, tacrolimus has not been shown to delay progression of joint damage on x-ray. In particular, treatment with cyclosporine plus MTX was shown to have a statistically significantly slower rate of disease progression on x-ray than MTX alone [37].

The adverse events with tacrolimus in RA patients are generally similar in nature to those observed with tacrolimus in transplant patients [101]. However, the incidence of adverse events such as hypertension, tremor, diabetes and increased creatinine level previously identified as safety concerns in transplant studies are generally notably lower in RA patients, and almost certainly the result of the lower dosage (3 mg/day) used to treat RA compared with that required to prevent transplant rejection (0.1–0.2 mg/kg/day). Comparison of the safety profiles of tacrolimus and its closest relative, cyclosporine, in RA patients suggests that tacrolimus has a lower incidence of the adverse events of abdominal pain, headache, nausea, hypertrichosis and dyspepsia, but has similar incidences of diarrhea, increased creatinine (30% or greater above baseline), hypertension and tremor (Table 3). Clinical trials of tacrolimus show rates of discontinuation for adverse events to be 13–20% [23,31], similar to those of the broad immunosuppressives, but higher than those of the biologics (3–13%) [2,33,36,38,39,45,48]. Of note, the combination of tacrolimus with MTX did not increase discontinuations for adverse events above that of tacrolimus alone [29,31,103]; however, in one double-blind, parallel group study, the combination of tacrolimus with MTX tripled discontinuations for adverse events above that seen for MTX alone [103]. Tacrolimus appears to be as well tolerated as most other combination therapies with broad immunosuppressives. As with other immunosuppressives, there is the possibility that tacrolimus may increase susceptibility to malignancies and lymphoproliferative disorders. In contrast to the biologics, there is no risk of injection site or infusion reactions; minimal potential for the development of an immune response against the therapeutic

Table 3. Adverse events reported in the product information for prescription rheumatoid arthritis drugs.

Adverse event	Percentage of patients experiencing adverse events							
	TAC 3 mg [101]*	*MTX* [106,107]‡	*LEF* [107]§	*CsA* [104]§	*TNF* [108–110]¶	*RIT + MTX* [111]#	*ABA* [112]**	*ANA* [113]§
Abdominal pain	7.8	8	6	15	5–12	11		5
Abnormal liver enzymes		10	5					
Lowered absolute neutrophil count								8
Accidental injury	6.5	11	5					
Allergic reaction		6						
Alopecia		6	10					
Anxiety						9		
Arthralgia		9			8	31		6
Asthenia	8.5	6		6	5–9	9		
Back Pain	4.6	9			8		7	
Bronchitis		7	7		10			
Chills						16		
Coughing		6		5	6–12		8	
Cramps	5.2							
Creatinine increased	↑ ≥30% BL: 30–40‡‡ ↑ ≥40% BL: 29‡‡			↑ ≥30% BL: 43§§ ↑ ≥50% BL: 24§§				
Diarrhea	13.7	20	17	12	12			7
Dizziness	7.2	5		8	7		9	
Dyspepsia	6.5	13	5	12	4–10	16	6	
Dyspnea				5				
Edema NOS				5				
Fever					7	27		
Flatulence				5				
Flu syndrome	16.3	7						6
Gastroenteritis		6						
GI abdominal pain		8	5					
Headache	9.2	21	7	17	12–18		18	12
Hypercholesterolemia						9		
Hypertension	7.8		10	8	5–7	43	7	
Hypertrichosis				19				
Infection				9	35	39		37
Infusion reaction						32		
Injection site reaction					8–37			71

**Incidence of adverse events occurring in ≥3% of treated patients.*

‡ Incidence of adverse events occurring in ≥5% of patients treated with MTX (from Arava® label).

§Incidence of adverse events occurring in ≥5% of treated patients.

¶Incidence of adverse events occurring in ≥5% of treated patients; includes patients on concomitant MTX.

#Incidence of adverse events occurring in ≥2% of treated patients, with an incidence ≥1% higher than in PBO.

***Incidence of adverse events occurring in ≥3% of treated patients, with an incidence ≥1% higher than in PBO (includes patients on other biologics).*

‡‡Incidence of patients with stated % increase above pretreatment baseline (BL) value; these incidence data were not reported as adverse events. Increased creatinine was reported as an adverse event in 3.7–6.7% of rheumatoid arthritis patients receiving tacrolimus at 3 mg/day.

§§Incidence of patients with stated % increase above pretreatment baseline (BL) value.

ABA: Abatacept; ANA: Aanakinra; BL: Baseline; CsA: Cyclosporine A; GI: Gastrointesinal; LEF: Leflunomide; MTX: Methotrexate; NOS: Nitric oxide synthase; PBO: Placebo; RIT: Rituximab; TAC: Tacrolimus; TNF: Tumor necrosis factor antagonists (etanercept, infliximab, adalimumab).

Table 3. Adverse events reported in the product information for prescription rheumatoid arthritis drugs (cont.).

Adverse event	Percentage of patients experiencing adverse events							
	TAC 3 mg [101]*	*MTX* [106,107]‡	*LEF* [107]§	*CsA* [104]§	*TNF* [108–110]¶	*RIT + MTX* [111]#	*ABA* [112]**	*ANA* [113]§
Leg cramps		6						
Migraine						9		
Mouth ulcer		10		7				
Nasopharyngitis							12	
Nausea	10.5	18	9	23	9–21	41		8
Pain		5		6	8			
Pain in extremity							3	
Paresthesia				8		12		
Pharyngitis					7–12	11		
Pruritis					7	26		
Rash	3.3	9	10	7	5–12		4	
Respiratory disorder					5			
Rhinitis					8–12	14		
Sinusitis	3.9	10			3–14			7
Tremor	8.5			8				
Upper respiratory infection		32	15		17–32	37		14
Urticaria						12		
Urinary tract infection	4.6		5		8		6	
Vomiting	5.2			9				

**Incidence of adverse events occurring in ≥3% of treated patients.*

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¶Incidence of adverse events occurring in ≥5% of treated patients; includes patients on concomitant MTX.

#Incidence of adverse events occurring in ≥2% of treated patients, with an incidence ≥1% higher than in PBO.

***Incidence of adverse events occurring in ≥3% of treated patients, with an incidence ≥1% higher than in PBO (includes patients on other biologics).*

‡‡Incidence of patients with stated % increase above pretreatment baseline (BL) value; these incidence data were not reported as adverse events. Increased creatinine was reported as an adverse event in 3.7–6.7% of rheumatoid arthritis patients receiving tacrolimus at 3 mg/day.

§§Incidence of patients with stated % increase above pretreatment baseline (BL) value.

ABA: Abatacept; ANA: Aanakinra; BL: Baseline; CsA: Cyclosporine A; GI: Gastrointesinal; LEF: Leflunomide; MTX: Methotrexate; NOS: Nitric oxide synthase; PBO: Placebo; RIT: Rituximab; TAC: Tacrolimus; TNF: Tumor necrosis factor antagonists (etanercept, infliximab, adalimumab).

agent; no increased risk of development of anti-double stranded antibodies or CNS demyelinating disease; and lower predisposition to the development of insidious infections like tuberculosis and serious infections such as sepsis.

Regulatory status

Tacrolimus has been approved in more than 70 countries, including the USA, Europe and Japan, for the prevention of allograft rejection in solid organ heart, liver and kidney transplantation. It is also approved in Japan for the prevention of graft-versus-host disease after allogeneic bone marrow transplant and for myasthenia gravis. It is available in capsule and solution formulations [101]. A topical formulation has recently been approved for the treatment of atopic dermatitis in several countries, including the USA. The T-cell-suppressing properties of tacrolimus have also made it an attractive candidate for the treatment of RA. On April 11, 2005, the Japanese Ministry of Health, Labor and Welfare approved oral tacrolimus hydrate for the treatment of RA in patients who respond insufficiently to other therapies, at an indicated dose of 3 mg/day (nonelderly patients) and 1.5 mg (starting dose) to 3 mg/day maximum dose (elderly patients) [114]. Tacrolimus 3 mg/day was approved as monotherapy for the treatment of RA by Health Canada in December 2004 for patients in whom DMARD therapy is inappropriate or ineffective [101]. It has not been approved in the USA for treatment of RA.

Conclusions & future perspectives

The potential role of tacrolimus in the treatment of RA has not been completely elucidated, owing in large part to the absence of head-to-head studies comparing tacrolimus with DMARDs. Tacrolimus has a very narrow therapeutic window and shows dose-dependent toxicity, particularly in the renal, digestive and nervous systems. The available efficacy data suggest that tacrolimus is less effective for symptomatic relief than MTX or biologic therapies, and it is too early to draw conclusions about the potential to inhibit radiographic progression. The incidences of adverse events associated with tacrolimus treatment in RA patients, alone or in combination with MTX, are lower than in patients treated with tacrolimus to prevent allograft rejection [101,102]. While the most common adverse events are gastrointestinal, the most clinically significant side effects are hypertension, tremors and elevations in serum creatinine. Some data from published studies have suggested that elevated creatinine levels do return to baseline, however, it is unclear whether serum creatinine elevations return to baseline in all patients, if so, how long they may take to return to baseline, and whether interruption of dosing aids the return. Careful monitoring of serum creatinine is required while on treatment [101]. The efficacy and safety of tacrolimus in RA have been studied for periods of up to 18 months. No data from studies are available regarding longer-term use of tacrolimus for this condition. Tacrolimus can be used in conjunction with NSAIDs and corticosteroids, and with MTX without concern for drug–drug interactions, although a regimen combining any of these drugs may impact renal function. In addition, its low cost and once-daily oral dosing regimen are attractive to patients. The biologics are also not without their efficacy and safety issues: loss of efficacy is seen in some patients, and there is predisposition to lymphoproliferative disease, insidious infections and serious infections. For some patients, tacrolimus provides substantial clinical benefit compared with other therapeutic options. For patients who do not respond to or cannot tolerate other available therapies, tacrolimus provides a reasonable, tested additional therapeutic option.

Although tacrolimus is not likely to be prescribed as first-line therapy for RA, it does have a place on the pharmacy shelf and will likely continue to retain a place, even as new therapies are introduced. The development of new therapies for RA, including biologics, is arduous and risky, and drugs targeting novel mechanisms often give unexpected clinical safety results, seen early (e.g., TeGenero's CD28 agonist) [54] or not until post-marketing (e.g., TNFα antagonists) [55]. The excitement that often accompanies new drug launches often fades as post-marketing data accumulate and safety issues not readily apparent from clinical trial results are revealed. Patients and their prescribers benefit from having well-characterized, long-marketed therapeutic options. The protest from rofecoxib patients and their prescribers when the NSAID was pulled from the American market in 2004 [115] serves as a reminder that clinical study results report population-based efficacy and safety data, but, on an individual patient level, a given drug may offer added clinical benefit and that all patients benefit from having multiple treatment options available.

Disclosure

The authors have served as consultants to Astellas.

Executive summary

Mechanism of action

- Tacrolimus (Prograf®) is an immunosuppressive macrolide calcineurin inhibitor isolated from the fermentation broth of *Streptomyces tsukubaensis* and is commonly used to prevent transplant rejection.
- Tacrolimus forms a complex with a T-cell cytoplasmic protein, FK-506 binding protein; this complex inhibits calcineurin, which in turn inhibits transcription of T-cell-derived inflammatory cytokines and decreases antigen-stimulated interleukin (IL)-2 T-cell production.
- The mechanism of action of tacrolimus is similar to that of cyclosporine, but the immunosuppressive potency of tacrolimus is 10- to 20-fold greater *in vivo* compared with cyclosporine.

Clinical efficacy

- The clinical efficacy of tacrolimus in rheumatoid arthritis (RA) most closely resembles that of cyclosporine.
- American College of Rheumatology (ACR) response rates observed with tacrolimus monotherapy are similar to those seen with cyclosporine and generally lower than those seen with other broad-based immunosuppressive and biologic therapies.
- ACR response rates observed with tacrolimus plus methotrexate (MTX) combination therapy are generally lower than those seen with MTX combined with other broad-based immunosuppressives or with biologics.
- Individual patients have achieved substantial and long-lasting benefit from tacrolimus therapy.
- Retardation of radiographic disease progression has not been shown for tacrolimus.

Executive summary

Safety

- The most common adverse events of tacrolimus monotherapy in RA patients are gastrointestinal in nature, but the most clinically significant are increased creatinine, tremor and hypertension.
- Incidences of adverse events seen in RA patients treated with tacrolimus plus MTX combination therapy are similar to the incidences observed with tacrolimus monotherapy.
- Tacrolimus has a renal safety profile similar to cyclosporine.
- Serum creatinine levels must be closely monitored during treatment.

Dosing recommendations

- Oral tacrolimus has recently been approved in Japan at doses of 1.5–3 mg/day and in Canada at a dose of 3 mg/day for the treatment of RA in patients who are refractory to other therapies.

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Affiliations

- *Benjamin D Schwartz, MD, PhD*
  The Camden Group, 19 Oak Park Drive
  St. Louis, MO 63141, USA
  Tel.: +1 314 220 7067;
  Fax: +1 314 432 5066;
  camden@camdengroup.com
- *Laurel J Mengle-Gaw, PhD*
  The Camden Group, 19 Oak Park Drive
  St. Louis, MO 63141, USA
  Tel.: +1 314 409 4093;
  Fax: +1 636 273 5614;
  camden@camdengroup.com