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Tacrolimus
In Patients with Rheumatoid Arthritis

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Contents

Abstract

▲ Tacrolimus, a hydrophobic macrolide with immunosuppressant properties, has recently been evaluated as a new treatment for adults with active rheumatoid arthritis.

▲ Oral tacrolimus 3mg once daily was significantly more effective than placebo in patients with rheumatoid arthritis (RA) who were refractory or intolerant to disease-modifying antirheumatic drugs (DMARDs), according to results from a 6-month, phase III trial; American College of Rheumatology 20 (ACR20) response rates were 27% and 10%. Tacrolimus 3mg once daily was effective in the same patient group in a 12-month, open-label trial; the ACR20 response rate was 38%.

▲ Oral tacrolimus 3mg once daily was effective in combination with established methotrexate therapy in patients with RA in a 6-month, open-label trial. The ACR20 response rate was 53%.

▲ Oral tacrolimus 3mg once daily was generally well tolerated by patients with active RA refractory or intolerant to previous DMARD treatment or when administered as combination therapy in patients with RA on established methotrexate therapy.

Features and properties of tacrolimus (FK506) [Prograf®]	
Indication	
Treatment of adults with rheumatoid arthritis (focus of this profile)	
Mechanism of action	
Immunosuppression via the inhibition of T-cell activation	
Dosage and administration	
Usual dosage	3 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (single dose of 3mg administered orally in adult patients with rheumatoid arthritis; mean values)	
Peak whole blood concentration	19.6 ng/mL
Time to peak whole blood concentration	1.3h
Area under the whole blood concentration-time curve	192.9 ng • h/mL
Bioavailability	≈25%
Elimination half-life	35.2h
Adverse events	
Most frequent	Diarrhoea, nausea, tremor, headache, abdominal pain, dyspepsia, increased creatinine, hypertension

Rheumatoid arthritis (RA) is characterised by symmetric, erosive synovitis, which leads to cartilage damage and joint destruction.[1] Recent evidence suggests that T cells play a central role in initiating and perpetuating the chronic autoimmune response in this disease. Cytokines such as tumour necrosis factor (TNF)-α, interleukin-1β and interleukin-6 have also been implicated in the immune responses that result in inflammation, pain and bone/cartilage destruction in joints.[2] Thus, the efficacy of therapies such as tacrolimus (FK506) [Prograf] [1] that suppress the activation of T cells and subsequent expression of cytokines has been investigated in patients with RA.

Tacrolimus is a hydrophobic macrolide isolated from *Streptomyces tsukabaenis* and has shown efficacy in the prevention of allograft rejection in solid organ transplant[3] and in the treatment of atopic dermatitis.[4] However, this review focuses on data relevant to the use of tacrolimus as an immunosuppressant in adult patients with RA.

1. Pharmacodynamic Properties

The pharmacodynamic properties of tacrolimus in various disease models,[3-6] have been reviewed previously.[6] This profile examines those pharmacodynamic properties relevant to patients with RA.

- Tacrolimus specifically suppresses T-cell activation.[7-9] Experimental evidence suggests that tacrolimus binds to the immunophilin FK506 binding protein-12 (FKBP-12).[7] A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is formed that inhibits the phosphatase activity of calcineurin. This prevents the activation of the nuclear factor of activated T cells, which is required for the expression of inflammatory cytokines.[6]
- *In vitro* studies demonstrated that tacrolimus specifically inhibited the production of TNFα,[10] interleukin-1β[10] and interleukin-6[11] triggered by T-cell activated human peripheral blood mononuclear cells.
- In animal models of arthritis[12-14] and in isolated human synovial cells,[15] tacrolimus reduced T-cell activation-induced production of inflammatory cytokine expression. Tacrolimus reduced elevated levels of TNFα,[12,13] interleukin-1β[12] and interleukin-6[12,14] in joint tissue in all stages of adjuvant-induced arthritis,[12] in joint tissue of collagen-induced arthritis[13] and in serum and joint tissue of peptidoglycan polysaccharide-induced polyarthritis.[14] Tacrolimus had an inhibitory effect on the expression of interleukin-6 in isolated human synovial cells.[15]
- Tacrolimus had no effect on lipopolysaccharide-induced cytokine production or proliferation of normal cells, such as bone marrow.[10]
- Prophylaxis with tacrolimus prevented the development of collagen-induced arthritis,[16] superantigen-potentiated collagen-induced arthritis[17] and adjuvant-induced arthritis[12,16] in animal models.
- Treatment with tacrolimus was effective in animal models of established arthritis. Tacrolimus suppressed inflammation,[13,14,18] reduced bone and cartilage damage[13] and recovered the loss of joint function[18,19] in animals in adjuvant-induced,[18,19] peptidoglycan polysaccharide-induced[14] or collagen-induced[13] arthritis.
- The analgesic action of tacrolimus on inflammatory pain was demonstrated in animal models of arthritis.[20] Tacrolimus rapidly reduced joint hyperalgesia, probably by downregulating interleukin-1β, even in the presence of severe inflammation.[20]
- Tacrolimus may exert favourable effects on bone or cartilage formation, via a calcineurin-independent mechanism.[6] Tacrolimus promoted osteogenic and chondrogenic differentiation in *in vitro* studies.[21,22] Tacrolimus induced differentiation of a mouse chondrogenic cell line[21] and enhanced osteoblastic differentiation in mesenchymal cells.[22] Moreover, tacrolimus increased bone formation in *in vivo* studies in rats.[23]
- Various nephrotic, diabetogenic, neurologic and cardiovascular effects have been associated with tacrolimus in solid organ transplant recipients (re-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

viewed by Staatz and Tett[5]). Limited data regarding nephrotoxic and cardiovascular adverse events in recipients of tacrolimus in patients with RA have been reported and are discussed in section 4.

2. Pharmacokinetic Properties

A study involving a single oral dose of tacrolimus 3mg in 12 adult patients (aged 25–76 years) with RA is reported in the manufacturer's prescribing information[7] and limited pharmacokinetic data after multiple-dose administration of once-daily tacrolimus 3mg are reported in open-label clinical trials in patients with RA[24,25] (see section 3 for further study design details). The pharmacokinetic properties of tacrolimus in healthy volunteers and in recipients of solid organ transplants have been extensively reviewed elsewhere.[5,26]

- After administration of a single 3mg dose of tacrolimus to patients with RA, the mean peak whole blood concentration (C_{max}) was 19.64 ng/mL after 1.3 hours.[7] The mean area under the whole blood concentration-time curve (AUC) was 192.88 ng • h/mL.
- Food reduced the rate and extent of tacrolimus absorption in 15 healthy volunteers.[7,27] When tacrolimus was administered with a high-fat meal, the mean AUC and C_{max} were decreased by 37% and 77% and the time to C_{max} (t_{max}) was lengthened 5-fold. With a high-carbohydrate meal, the mean AUC and C_{max} were decreased by 28% and 65%.
- After multiple-dose administration of once-daily tacrolimus 3mg, median trough whole blood concentrations of tacrolimus were 2–3 ng/mL, with no tacrolimus accumulation, in 896 patients with RA who had discontinued disease-modifying antirheumatic drugs (DMARDs) [treatment for up to 18 months][24] and in 80 patients who were receiving concomitant methotrexate (6 months of treatment).[25]
- Tacrolimus is a highly lipophilic substance, with oral absorption being dissolution rate-limited; however, absorption is independent of bile flow.[27] The absolute bioavailability of tacrolimus is approximately 25% in adult patients with RA.[7]
- Tacrolimus binds extensively to erythrocytes, resulting in a mean distribution ratio of whole blood/plasma concentrations of 35 (range 12–67).[27] In the plasma, the drug is highly bound to plasma proteins (approximately 99%), mainly α1-acid glycoprotein and serum albumin. Partitioning of tacrolimus between red blood cells and plasma is also affected by the drug concentration, haematocrit, sample temperature and plasma protein concentration.[7,27]
- The apparent volume of distribution of tacrolimus in adult patients with RA is 2.37 L/kg (based on whole blood concentrations).[7]
- Tacrolimus is extensively metabolised by demethylation and hydroxylation (mainly by cytochrome P450 (CYP) 3A isoenzymes in the liver and intestinal wall),[5,26] with <1% of the unchanged drug excreted in the urine.[7,27] Eight metabolites have been characterised using *in vitro* models, with only one metabolite (a 31-demethyl metabolite) showing significant immunosuppressive activity.[7,27] After oral administration of [^{14}C]-labelled tacrolimus to healthy volunteers, 93% of the administered dose was recovered in the faeces, indicating that excretion is primarily via the biliary route.[26]
- Systemic clearance of tacrolimus is 0.049 L/h/kg in adult patients with RA.[7]
- The terminal elimination half-life of oral tacrolimus in patients with RA is long (35.2 hours), thereby allowing once-daily administration.[7]
- Since tacrolimus is metabolised by the CYP3A isoenzymes, drugs interacting with these systems may affect the pharmacokinetics of tacrolimus.[7,26,27] The CYP3A inhibitors that may potentially increase whole blood tacrolimus concentrations include various calcium channel antagonists (diltiazem, nicardipine, nifedipine, verapamil), imidazole antifungal agents (clotrimazole, fluconazole, itraconazole, ketoconazole), macrolide antibacterial agents (clarithromycin, erythromycin, troleandomycin), gastrointestinal prokinetic agents (cisapride and metoclopramide) and other drugs (e.g. bromocriptine, cimetidine, omeprazole, ethinylestradiol, methylprednisolone). Enzyme inducers that may decrease tacrolimus blood concentrations include certain anticonvulsants, as well as the antibac-

terials rifabutin and rifampicin.[7,26,27] St John's wort (*Hypericum perforatum*) may also reduce tacrolimus blood concentrations.[7]

- No pharmacokinetic interaction was reported between tacrolimus and methotrexate in patients with RA.[28]

3. Therapeutic Use

The efficacy of once-daily oral tacrolimus has been investigated as monotherapy in patients with active RA refractory or intolerant to DMARDs[24,29-31] or as combination therapy in patients with active RA established on methotrexate.[25]

In patients who had discontinued DMARDs (drug not stated[24,29,31] or methotrexate[30]), tacrolimus was administered as monotherapy in three (two dose-ranging phase II[29,30] and one phase III[31]) 6-month, randomised, double-blind, placebo-controlled, multicentre trials and in a 12-month open-label study.[24]

In the dose-ranging trials,[29,30] patients were randomised to receive once-daily tacrolimus 1,[30] 1.5,[29] 3[29,30] or 5mg[30] or placebo.

In the phase III trial,[31] patients were randomised to once-daily tacrolimus 2 or 3mg or placebo; 464 patients received at least 1 dose of the study drug and the study was completed by 144 (46.9%) recipients of tacrolimus and 45 (28.7%) recipients of placebo. DMARDs were discontinued 4 weeks prior to screening[30,31] or patients were switched to the study drug without a washout period.[29]

In the 12-month open-label trial (median duration 359 days),[24] 896 patients received at least one dose of once-daily tacrolimus 3mg; 211 patients who had previously been treated with tacrolimus 2 or 3mg once daily were rolled over from the phase III trial[31] and 685 patients (585 patients directly enrolled and 100 patients who had received placebo were rolled over from the phase III trial[31]) who had discontinued all DMARDs for ≥2 weeks and had at least five tender/painful joints and three swollen joint were enrolled *de novo*. The study was completed by 489 (54.6% of patients). Overall, 651 patients had ≥6 months, 497 patients had ≥12 months and 54 patients had 18 months of treatment with tacrolimus 3mg once daily.

Once-daily tacrolimus 3mg was administered as combination therapy in 80 patients with active RA established on methotrexate therapy (5–20 mg/week for ≥1 month) in a 6-month open-label trial.[25]

Efficacy was assessed according to the American College of Rheumatology (ACR) response rate.[32] The primary endpoint was generally the ACR20 response rate at treatment end; an ACR20 is a combined index of response that requires ≥20% improvement in both the tender and swollen joint counts plus a ≥20% improvement in three of the following parameters: patient's or physician's global assessment of disease activity, patient's global assessment of pain, acute-phase reactant levels (erythrocyte sedimentation rate or C-reactive protein) or patient's assessment of physical function (based on the modified Health Assessment Questionnaire). Although the ACR20 response rate was the primary efficacy endpoint in the 6-month, open-label, multicentre trial in patients receiving concomitant methotrexate[25] and in the 12-month open-label trial in patients who had discontinued DMARDs,[24] tolerability (section 4) was the primary focus of these trials. Secondary endpoints included ACR50 and ACR70 response rates at treatment end and the percentage change from baseline in the various individual ACR component scores at the end of treatment.

Patients enrolled in these trials were aged ≥16 years and had active RA according to ACR criteria[32] for at least 6 months and were ACR functional class I–III as defined by revised ACR criteria.[33] Concomitant administration of NSAIDs and oral corticosteroids was permitted.

- The ACR20 response was dose related in tacrolimus recipients. In the larger of the dose-ranging studies,[30] the ACR20 response rate was 15.5% in placebo recipients compared with 29.0% ($p < 0.058$), 34.4% ($p < 0.013$) and 50.0% ($p \leq 0.001$) in recipients of tacrolimus 1, 3 or 5mg once daily (assessed in the intent-to-treat population [n = 268]). In the other dose-ranging study,[29] the ACR20 response rate was 14.1% in placebo recipi-

ents compared with 24.6% and 48.3% ($p < 0.001$ vs placebo) in recipients of tacrolimus 1.5 or 3mg once daily (assessed in the per-protocol population [n = 179]).[29]

- In the phase III trial,[31] the ACR20 response rate in patients with active RA who had completed 6 months of therapy was significantly higher with once-daily tacrolimus 3mg (26.8%; $p < 0.0005$) or 2mg (18.8%; $p < 0.05$) than placebo (10.2%). ACR20 response rates at the end of treatment are shown in figure 1. ACR20 response rates in tacrolimus recipients increased over time, with the ACR response rates in tacrolimus recipients being significantly different to that in placebo recipients in the last 3 months of the study.

- Long-term treatment with tacrolimus 3mg once daily (up to 18 months[24]) resulted in a higher ACR20 response rate than that obtained after 6 months.[31] The overall ACR20 response rate with tacrolimus 3mg once daily at the end of a 12-month, open-label trial was 38.4%.[24] In the individual treatment groups, ACR20 response rates were 35.9% in the *de novo* group (total of 12 months of treatment with tacrolimus 3mg once daily), 44.7% in the treatment group who had previously received tacrolimus 2mg once daily in the phase III trial (total of 12 months of treatment with tacrolimus 3mg once daily) and 48.1% in patients who had previously received tacrolimus 3mg once daily in the phase III trial (total of 18 months of treatment with tacrolimus 3mg once daily).[24]

- The highest ACR response rates associated with treatment with tacrolimus 3mg once daily were reported in patients with active RA who received concomitant methotrexate treatment; ACR20 response rates were 52.5% at the end of the 6-month, open-label trial.[25] Response rates were similar in recipients of low-dose (5–12.5 mg/week) and high-dose (15–20 mg/week) methotrexate.

- In recipients of 6 months of tacrolimus 3mg once daily, ACR50 and ACR70 response rates at the end of treatment were 11.8% and 3.3% in those who had discontinued DMARDs (phase III trial; figure 1[31]) and 28.8% and 13.8% in those who continued to receive concomitant methotrexate (open-label trial).[25] ACR50 and ACR70 response rates at treatment end in the 12-month, open-label trial in patients who had discontinued DMARDs were 18.6% and 9.0%.[24]

- Individual ACR scores also improved with tacrolimus therapy. In patients who had discontinued DMARDs, the median percentage improvement in all individual ACR component scores was significantly greater in recipients of tacrolimus 3mg once daily than placebo (phase III trial; figure 2).[31] Notably, the median percentage change from baseline in both the tender/painful and swollen joint counts were significantly greater in recipients of tacrolimus 3mg once daily (both −30%) than placebo (−2% and −6%; both $p < 0.001$). In the 12-month open-label trial, swollen joint count improved by ≥20%, ≥50% and ≥70% in 61.8%, 43.9% and 26.1% of patients, respectively, at treatment end.[24] The respective improvements in tender or painful joint count occurred in 61.5%, 46.4% and 32.1% of patients. In the 6-month open-label trial in recipients of tacrolimus 3mg once daily and methotrexate,[25] a ≥50% improvement in the number of tender/painful joints occurred in 67.5% of patients and a ≥50% improve-

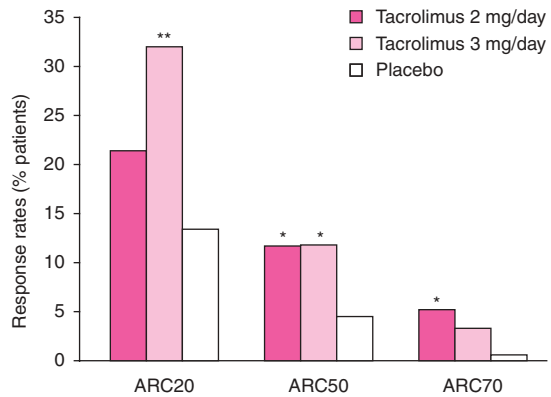

Fig. 1. American College of Rheumatology (ACR) response rates at end of treatment (last observation carried forward) in patients with active rheumatoid arthritis resistant or intolerant to disease-modifying antirheumatic drugs.[31] In the 6-month, double-blind, multicentre trial, patients were randomised to placebo (n = 157), tacrolimus 2mg once daily (n = 154) or tacrolimus 3mg once daily (n = 153). Concomitant administration of NSAIDs and oral corticosteroids was permitted. **ACR20, 50 and 70** = ACR improvements of 20%, 50% and 70%, respectively; * $p < 0.05$, ** $p \leq 0.0001$ vs placebo.

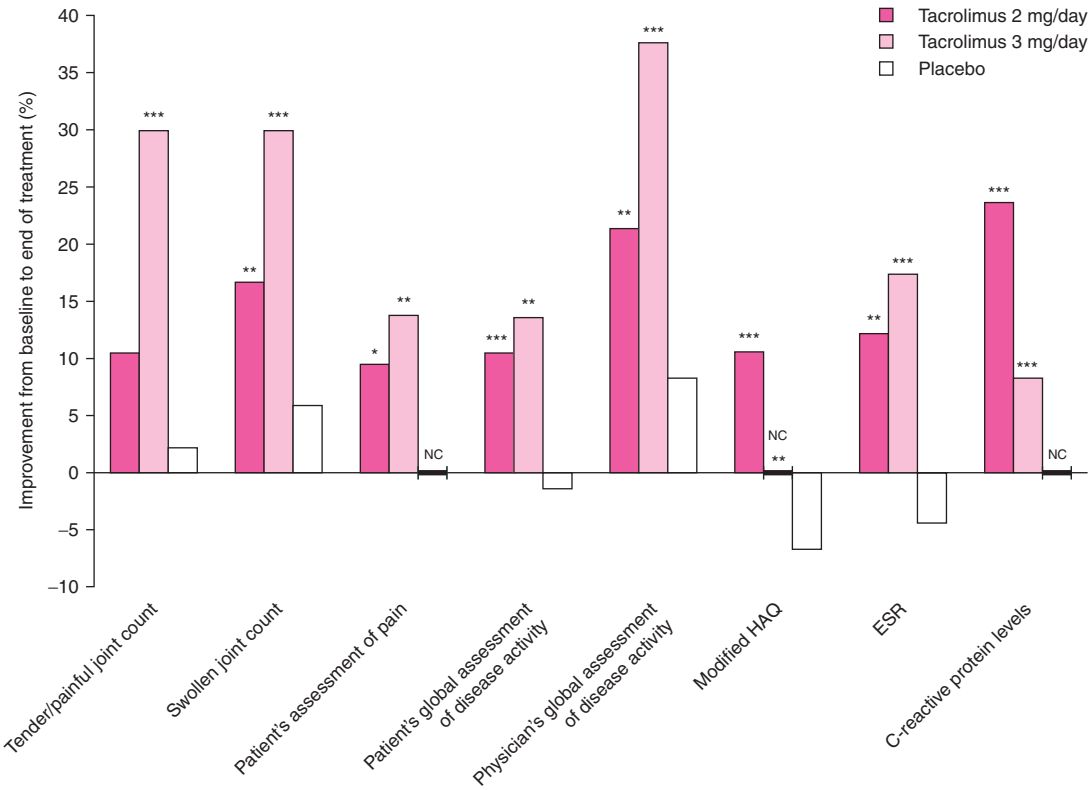

Fig. 2. Improvement from baseline to treatment end in the individual American College of Rheumatology component scores in patients with rheumatoid arthritis intolerant or resistant to disease-modifying antirheumatic drugs.[31] In the 6-month, double-blind, multicentre phase III trial, patients were randomised to placebo (n = 157), tacrolimus 2mg once daily (n = 154) or tacrolimus 3mg once daily (n = 153). Concomitant administration of NSAIDs and oral corticosteroids was permitted. Calculations were based on the last observation carried forward method. The patient's assessment of pain, the patient's and physician's global assessment of disease activity were measured on a 100mm visual analog scale. **ESR** = erythrocyte sedimentation rate; **HAQ** = Health Assessment Questionnaire (part 1 A–H); **NC** = no change; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

ment in the number of swollen joints occurred in 60% of patients.

4. Tolerability

Monotherapy

The tolerability of monotherapy with tacrolimus 3mg once daily has been investigated in 6-month, randomised, double-blind trials[29-31] and in a 12-month open-label trial[24] in patients with RA who had discontinued DMARDs (see section 3 for further study design details).

- Tacrolimus was generally well tolerated.[24,29-31]
- In a 6-month, randomised, double-blind trial, adverse events were reported at least once in >80% of tacrolimus recipients versus 72% of placebo recipients ($p < 0.05$).[31] Of the adverse events reported, diarrhoea was more common with tacrolimus than with placebo.
- The incidences of hypertension, tremor, diabetes mellitus and increased creatinine levels were 7.8%, 8.5%, <5% and 6.5% in patients with RA treated with tacrolimus 3mg once daily in the trial.[31] Higher incidences of these adverse events has been reported in trials in renal and liver transplant recipients (38–50%, 48–56%, 24% and 24–45%, respectively; data reported in Yocum et al.[31]), but this

reflects the higher dosage of tacrolimus required to prevent transplant rejection (0.1–0.2 mg/kg/day).

- Common treatment-emergent adverse events reported in the 12-month open-label trial are shown in figure 3. At least one treatment-emergent adverse event was reported in 59% of patients. Withdrawal as a result of an adverse event that was possibly or probably related to treatment occurred in 16.2% of tacrolimus recipients. No adverse event with an incidence >0.7% was reported for the first time after 3 months of treatment.

- One or more serious adverse event possibly or probably related to treatment was reported in 2.7% of patients receiving tacrolimus 3mg once daily and included pneumonia (0.6%), hyperglycaemia (0.3%), gastroenteritis (0.2%), pancreatitis (0.2%) and diabetes (0.2%) in the 12-month trial.[24]

- The mean creatinine level increased from 0.76 mg/dL at baseline to 0.85 md/dL at treatment end ($p < 0.0001$; data from 872 patients) in this study.[24] Creatinine levels remained within the normal range in 92% of the 872 patients. Maximum increases in creatinine levels ≥30% from baseline occurred in 40% of patients during treatment and in 20% of patients at treatment end.

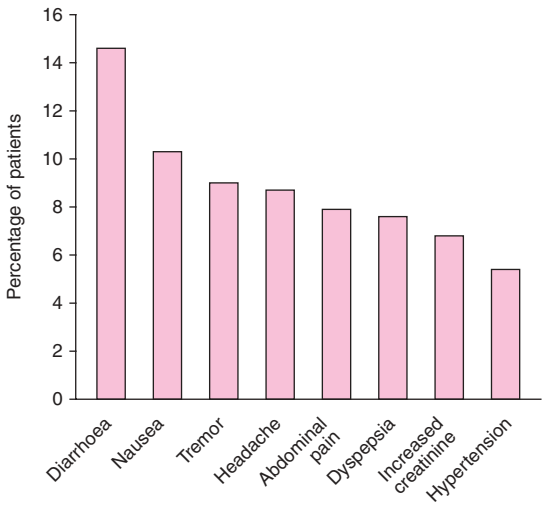

Fig. 3. Common treatment-emergent adverse events (≥5% of patients) possibly or probably related to tacrolimus 3mg once daily in patients with active rheumatoid arthritis.[24] In this open-label trial, patients received a median 359 days of tacrolimus treatment. All treatment with disease-modifying antirheumatic drugs were discontinued, but concomitant administration of NSAIDs and oral corticosteroids was permitted. At least one dose of tacrolimus was received by 896 patients; 211 patients who had previously been treated with tacrolimus 2 or 3mg once daily were rolled over from a phase III trial[31] and 685 patients who were enrolled *de novo*.

- Mean BP increased from 128.5/78.3mm Hg at baseline line to 129.7/79.5mm Hg at treatment end; while the increase in diastolic blood pressure was statistically significant ($p = 0.0009$), it was not considered to be clinically relevant.[24]

- Diabetes was considered possibly or probably related to treatment in <1% of tacrolimus recipients in the 12-month trial.[24] At some point during the study, glucose levels were >150 mg/dL in 16% of patients and glycosylated haemoglobin (HbA_{1c}) levels were >6.5% in 21% of patients.

Combination Therapy

The tolerability of oral tacrolimus 3mg once daily in combination with established methotrexate therapy was investigated in 80 patients with active RA in a 6-month, multicentre, open-label study (see section 3 for further study design details).[25]

- At least one treatment-emergent adverse event was reported by 86.3% of patients, with a similar incidence in patients who received high-dose (15–20 mg/week; $n = 45$) or low-dose (5–12.5 mg/week; $n = 35$) methotrexate. Ten patients (12.5%) withdrew because of an adverse event probably or possibly related to tacrolimus treatment. One serious adverse event (pancreatitis) was possibly related to tacrolimus therapy.[25]

- The mean creatinine level increased from 0.74 mg/dL at baseline to 0.81 mg/dL at treatment end ($p < 0.001$). Maximum increases in creatinine levels ≥30% from baseline occurred in 29% of patients during treatment and in 15% of patients at treatment end, with 3.8% exceeding the normal range.[25]

- Hypertension was reported in 3.8% of patients.[25] The mean change in diastolic and systolic BP was −0.3mm Hg and −1.4mm Hg, respectively. No patients withdrew from the study as a result of hypertension.

- Hyperglycaemia (blood glucose levels >150 mg/dL) was reported in two patients (3%) who had a history of diabetes.[25] Four patients who had been

treated with tacrolimus and high-dose methotrexate reported HbA_{1c} >6.5%; one of these patients had a history of diabetes.

5. Dosage and Administration

Oral tacrolimus was generally administered at a dosage of 3mg once daily in well designed clinical trials in adult patients with RA for whom DMARD therapy was ineffective or inappropriate and in adult patients with RA receiving concomitant methotrexate (see section 3).

Tacrolimus may be used in combination with NSAIDs and/or corticosteroids.[7] Careful monitoring (including serum creatinine levels) of tacrolimus recipients is required.[7] Physicians are warned that increased susceptibility to infection and the possibility of lymphoma may result from immunosuppression.[7,27]

6. Tacrolimus in Patients with Rheumatoid Arthritis: Current Status

Oral tacrolimus 3mg once daily was first approved for use in Canada for administration to adult patients for whom DMARD therapy is ineffective or inappropriate.[7] Oral tacrolimus 3mg once daily has also recently been approved in Japan for use in adult patients with RA in whom existing therapy is ineffective; the approved dosage for use of this agent in elderly patients with RA is 1.5mg once daily. The drug is in phase III and phase II trials, respectively, in the US and Europe for patients with RA.

Oral tacrolimus 3mg once daily was significantly more effective than placebo in patients with RA who were refractory or intolerant to DMARDs enrolled in a 6-month, phase III trial. The ACR20 response rate with tacrolimus 3mg once daily in a 12-month, open-label trial were higher than that in the 6-month phase III trial. Treatment with tacrolimus 3mg once daily (for up to 18 months) was also generally well tolerated in this patient group. Oral tacrolimus 3mg once daily was effective and generally well tolerated in patients with active RA established on methotrexate therapy in a 6-month, open-label trial.

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