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Original Article

Effectiveness and Safety of Tacrolimus in Patients with Active Rheumatoid Arthritis with Inadequate Response to Disease-modifying Anti-rheumatic Drugs: The TREASURE Study

Dong Hyuk Sheen[1], Seung Jae Hong[2], Sang Heon Lee[3], Hye Soon Lee[4], Won Tae Chung[5], Hongsi Jiang[6], Sungmin Lee[7], Dae Hyun Yoo[8]

[1]Division of Rheumatology, Eulji University Hospital, Daejeon, [2]Division of Rheumatology, Kyung Hee University Medical Center, Seoul, [3]Division of Rheumatology, Konkuk University Medical Center, Seoul, [4]Division of Rheumatology, Hanyang University Guri Hospital, Guri, [5]Division of Rheumatology, Dong-A University Hospital, Busan, Korea, [6]Medical Affairs Asia Oceania, Astellas Pharma, Inc., Singapore, [7]Medical Affairs, Astellas Pharma Korea, Inc., [8]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

Objective. Evaluate effectiveness/safety of tacrolimus in patients in Korea with active rheumatoid arthritis (RA) and unsuccessful response to disease-modifying anti-rheumatic drugs (DMARDs). **Methods.** Open-label, single-arm, non-comparative, 24-week, Phase-IV study in patients with active RA who had taken DMARDs for >6 months. Following a washout period, tacrolimus was initiated (baseline–12 weeks; dose 2 mg/day and 1.5 mg/day in patients aged ≤65 and >65 years, respectively). After 12 weeks, dose could be adjusted (remaining between 1~3 mg); treatment continued to 24 weeks. Primary endpoint was American College of Rheumatology 20% improvement (ACR20) (baseline–Week 24). Secondary endpoints included ACR50/ACR70 response, disease-activity score in 28 joints (DAS28) erythrocyte sedimentation rate (ESR), number of tender/swollen joints, and bone mineral density (BMD) loss. Adverse events (AEs) were recorded. **Results.** Overall, 121 patients were analysed. Mean ±standard deviation tacrolimus dose baseline–Week 24 was 1.81±0.47 mg/day. After 24 weeks, 64.5%, 39.7%, and 19.0% of patients were ACR20, ACR50, and ACR70 responders, respectively. DAS28-ESR score decreased from 5.5±0.8 (baseline) to 3.7±1.5 (Week 24; $p<0.0001$); number of tender/swollen joints decreased. Between screening and Week 24, change in BMD-T score in lumbar and femur regions was −0.06±0.38 ($p=0.1550$) and −0.04±0.28 ($p=0.0936$), respectively, with no significant change in International Society for Clinical Densitometry classification. Fifty-six (46.3%) patients experienced 93 AEs; 75.3% were mild. No unexpected safety signals identified. **Conclusion.** Tacrolimus therapy was associated with a high proportion of ACR responders, and improved DAS28-ESR score and physical joint function during the study. Tacrolimus may be a suitable therapy for DMARD-resistant patients with RA. **(J Rheum Dis 2019;26:20-30)**

Key Words. Anti-rheumatic, Bone density, Osteoporosis, Rheumatoid arthritis, Tacrolimus

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that is characterised by synovial inflammation and hyperplasia, autoantibody production, and cartilage and bone destruction [1]. RA is also associated with systemic features, including skeletal, cardiovascular, pulmonary, and psychological disorders [1], and patients with the disease have a 2.6 fold higher mortality rate than the general population [2]. In the treatment of RA, it is important to decrease inflammation, protect joint structure, and preserve the patient's performance in daily activities.

Drug therapy is an essential component for the manage-

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Corresponding to : Dae Hyun Yoo http://orcid.org/0000-0002-0643-4008
Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea. E-mail : dhyoo@hanyang.ac.kr

ment of RA. Indeed, it is recommended to initiate treatment with disease-modifying anti-rheumatic drugs (DMARDs) as soon as a diagnosis of RA is made, and methotrexate is typically the first choice [3]. However, patients may experience methotrexate-related toxicity, such as gastrointestinal disorders and hair loss, which may be exacerbated by add-on therapy [4,5]. In patients for whom DMARDs are inappropriate or have failed, biological agents, such as tumour necrosis factor (TNF) inhibitors, are recommended [3]. Nevertheless, approximately 30% of patients receiving an anti-TNF agent fail to achieve at least a 20% improvement in the American College of Rheumatology (ACR) criteria for RA, and effectiveness of therapy can decrease with time [6,7]. In such patients, another immune modulator may be indicated [3]. For example, tacrolimus could be useful for patients with an inadequate response to DMARDs, and who do not have poor prognostic factors according to the European League Against Rheumatism (EULAR) 2016 recommendations for the management of RA [3].

It is well known that T lymphocytes are critical to the pathogenesis of systemic rheumatic disease, and imbalances in the numbers and functions of specific T-cell subsets may play a role [8]. Tacrolimus is an immunosuppressive macrolide that blocks T-cell activation by specifically inhibiting calcineurin [9]. While a potential toxic effect of this macrolide on osteoblasts has been reported in vitro [10], tacrolimus is thought to have a protective effect on bone via anti-inflammatory mechanisms [11], thus indicating its potential as a therapy for RA. Tacrolimus was approved in Canada in 2004 for the treatment of patients with RA and an inadequate response to conventional therapies, and was subsequently approved for RA in Japan, Korea, and other regions, including Hong Kong. While the safety and efficacy of tacrolimus in RA has been demonstrated in several clinical trials [12-14], there remain limited data on the use of tacrolimus as the main treatment in patients with RA. Furthermore, there are few studies for the use of tacrolimus in patients with RA in Korea. This study evaluated the effectiveness and safety of tacrolimus in patients with active RA in Korea, who had an unsuccessful response to DMARDs.

MATERIALS AND METHODS

Study design and patients

This was an open-label, single-arm, non-comparative, 24-week, Phase IV study conducted at six medical centres in Korea (ClinicalTrials.gov NCT01511003). The study was carried out in accordance with the Declaration of Helsinki, and the trial protocol was reviewed and approved by the relevant Institutional Review Boards. All patients provided written informed consent before starting the study.

Patients aged >20 and <75 years at screening, with active RA for >6 months, based on the ACR 1987 classification, and normal electrocardiogram evaluations were included if they had taken one or more DMARDs (including methotrexate) for >6 months. At screening, patients were required to have an erythrocyte sedimentation rate (ESR) ≥28 mm/h, or C reactive protein (CRP) ≥1.0 mg/dL, six or more tender joints in the 68 interest joints, and three or more swollen joints in the 66 interest joints.

Patients were excluded if they had previously received tacrolimus (except as topical application), had a renal disorder, or serum creatinine >1.4 mg/dL, had viral hepatitis, hepatic cirrhosis, or serum glutamate oxaloacetate transaminase/serum glutamate pyruvate transaminase >2x upper limit of normal at screening, or had pancreatitis, a history of impaired glucose tolerance, or glycated haemoglobin >6.4%. A full list of exclusion criteria can be found at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01511003?term=PRGRA-10-04-KOR&rank=1).

Patients were permitted to continue a maximum of two of the following DMARDs: methotrexate, hydroxychloroquine, or sulfasalazine. Prior to the study treatment phase, a washout period of 4 weeks was required for each DMARD that was stopped. A washout period was also mandatory for patients who had received biological agents (etanercept and adalimumab, 4 weeks; infliximab, 8 weeks; rituximab, 6 months). Patients receiving leflunomide could be enrolled 48 hours after taking 8 g of three-times-daily cholestyramine for 11 days (a 12-week washout period was needed if there were difficulties taking cholestyramine). Patients attended five clinic visits: screening (Day −180 to −1, according to required washout period; Visit 1), baseline (Day 0; Visit 2), and at Weeks 4 (Visit 3; ±7 days), 12 (Visit 4; ±7 days), and 24 (Visit 5; ±7 days). The investigator checked for compliance with the washout period before administration of study drug at Visit 2.

Treatment

Tacrolimus (Prograf; Astellas Pharma Ltd, Chertsey,

UK) therapy was initiated at baseline (Day 0) with an initial dose of 2 mg/day in patients aged ≤65 years, or 1.5 mg/day in patients aged >65 years. Tacrolimus was taken once daily after dinner, with sufficient water. After 12 weeks of administration, the dose could be adjusted (remaining within 1~3 mg/day), at the investigator's discretion, and treatment was continued up to 24 weeks.

During the study, patients were not permitted to receive DMARDs (with the exception of methotrexate, hydroxychloroquine, and sulfasalazine, as detailed above). Other prohibited concomitant medications included anti-TNF, other immunosuppressants (except azathioprine and mizoribine, which could be taken), steroid injection, and oral steroids ≥10 mg/day (continuation of oral steroids <10 mg/day was permitted with dose adjustments, according to the judgement of the investigator). New administration of oral steroids, and chondroprotectants was also prohibited. Acetaminophen (including tramadol/acetaminophen compounds) was permitted only for an adverse event (AE) or aggravated pain, at a dose <2,600 mg/day or 13,000 mg/week. Patients were instructed not to take acetaminophen within 24 hours before each visit. Permitted treatments without dose limitations included drugs for treatment of diseases other than RA, steroids for topical use, non-steroidal anti-inflammatory drugs (NSAIDs), other anti-inflammatory analgesic drugs/narcotics, physical therapy, and osteoporosis agents.

Measurements

At screening, the ACR functional class was determined by the investigator according to ACR functional classification criteria [15]. Across all visits, joint tests were used to evaluate the severity of RA, and included tender joint counts (68 joints), and swollen joint counts (66 joints). A visual analogue scale (VAS) was used by patients to evaluate their pain (0=no pain, to 100=extreme pain), fatigue (0=very well, to 100=very poor), and activity (0=very well, to 100=very poor); activity was also assessed by investigators.

Disease activity score in 28 joints (DAS28) was calculated across visits [16], using patient global health (patient self-assessment), tender and swollen joint counts, and ESR. The acute phase reactant CRP was also measured.

Bone mineral density (BMD) was measured using dual energy X-ray absorptiometry at screening and at Week 24, with the Hologic Discovery W (two sites), Lunar I-DXA (two sites), Hologic DELPHI W (one site), and Hologic QDR (one site). Bone turnover marker tests (bone-specific alkaline phosphatase, osteocalcin, c-telopeptide, receptor activator of nuclear factor-κB ligand, and osteoprotegerin) were carried out at baseline and Week 24. In addition, compliance with tacrolimus medication was assessed using the following equation:

$$\text{Drug compliance (\%)} = \frac{\text{Amount of drug taken}}{\text{Amount of drug that should have been taken}} \times 100$$

AEs were recorded across visits. Serious AEs were those that resulted in death or were life threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; were persistent or resulted in significant disability/incapacity; and/or resulted in a congenital abnormality/birth defect. An AE was also considered serious if it jeopardised the patient, or if an internal or surgical intervention was required to prevent one of the other outcomes previously listed from occurring. Patients could be discontinued from the study due to a serious AE at the investigator's discretion.

Endpoints

The primary endpoint was ACR20 response. Secondary efficacy endpoints included ACR50 and ACR70 response. The DAS28-ESR response was also recorded, defined as good (improvement of >1.2 points from baseline to Week 24, and a score ≤3.2 at Week 24), moderate (improvement of >0.6 to ≤1.2 points, and a score of ≤5.1, or an improvement of >1.2 points and a score of >3.2), or non response (improvement of ≤0.6 points, or improvement >0.6 to ≤1.2 points and a score of >5.1). The rate of BMD loss was compared between screening and Week 24, where T score (lumbar, femur) was classified as normal (score ≥−1.0), osteopenia (score ≥−2.5 to <−1.0), or osteoporosis (<−2.5). Other efficacy endpoints included the change in bone turnover marker levels between baseline and Week 24, as well as changes in the number of tender and swollen joints, VAS scores, and acute phase reactant levels.

Safety endpoints were AEs, including those considered to be related to study drug.

Sample size and statistics

Based on an ACR20 response of 48.5%, as reported by

Kawai et al. [17], 96 patients were required to estimate the response rate in this study within 10% of the true value, with 95% confidence. Assuming a 25% drop-out rate, the aim was to recruit 128 patients. The intention-to-treat (ITT) population and safety-analysis set (SAF) consisted of all patients who received at least one dose of study drug, and the per protocol (PP) population comprised all patients in the ITT population who completed the study, without major protocol violation. Efficacy evaluations were primarily conducted in the ITT population, with supporting analyses in the PP population. Patient demographics, baseline characteristics, and dosing data were split by patient age ≤65 years versus >65 years, due to the different initial daily dose of tacrolimus between these age groups according to the indication in Korea (1.5 vs. 2.0 mg, respectively).

ACR20, ACR50, and ACR70 were evaluated as the proportion of responders, with 95% confidence interval (CI). The change in DAS28-ESR and BMD between baseline and Week 24 was assessed with a Wilcoxon signed rank test. In order to compare the difference in BMD-T score classifications between screening and Week 24, McNemar's test was used. Statistical tests were two-tailed, with a significance level of 0.05. For missing efficacy values, the last observation carried forward method was applied. Statistical analyses were performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Overall, 160 patients were screened at six medical centres, of whom 36 patients were not enrolled due to screening failures (Figure 1). Of the 124 patients enrolled (aged ≤65 years, n=108; >65 years, n=16), 99 completed the study. The date of first enrolment was 5 December 2011, and the date of last evaluation was 11 May 2015.

Regarding the analysis populations, of the 124 patients enrolled, three did not receive tacrolimus therapy; therefore, 121 patients formed the ITT population/SAF (aged ≤65 years, n=106; >65 years, n=15). Among the 121 patients in the ITT population, 99 completed the study; however, as two patients did not strictly meet the definition for the PP population, and were excluded, 97 patients formed the PP set (aged ≤65 years, n=89; >65 years, n=8).

Patient baseline demographics and characteristics are presented in Table 1 (ITT population). The mean±standard deviation (SD) age of patients was 54.7±9.7 years, and 88.4% were female. Patients had RA for a mean±SD duration of 93.2±81.0 months (range 7~416 months). As expected, patients aged >65 years had RA for longer than those aged ≤65 years (136.1±108.5 vs. 87.0±73.8 months, respectively), and a greater proportion had ACR functional class III. All patients had electrocardiograms, glycated haemoglobin levels, antigen levels of the hep-

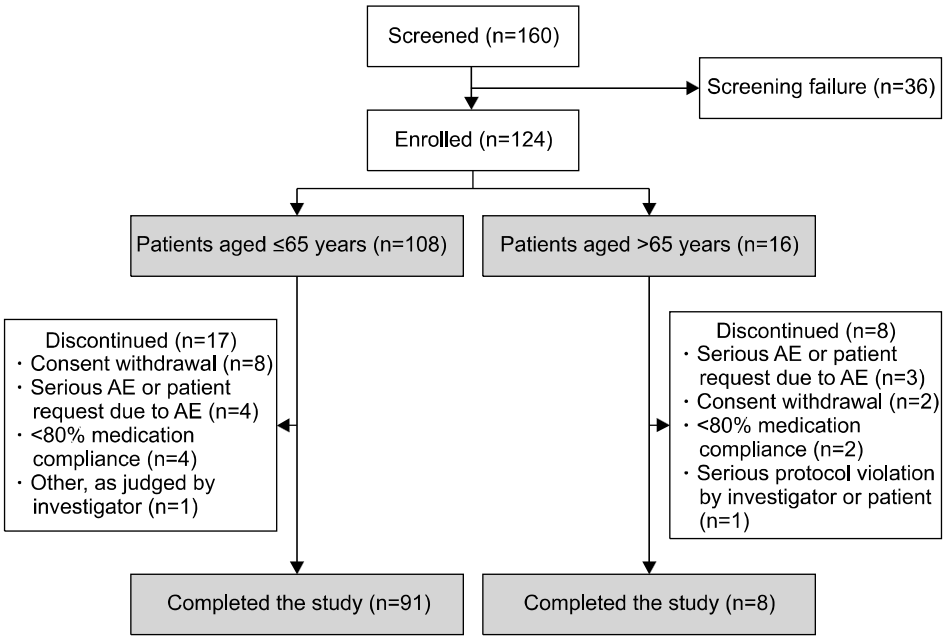

Figure 1. Patient flow through the study. AE: adverse event.

Table 1. Patient demographics and baseline characteristics, overall and stratified by patient age (≤65 years vs. >65 years) (ITT population)

Characteristics	Patients aged ≤65 years (n=106)	Patients aged >65 years (n=15)	All patients (n=121)
Female sex	93 (87.7)	14 (93.3)	107 (88.4)
Age (yr)	52.7±8.5	69.3±2.6	54.7±9.7
Height (cm)	157.3±6.6	152.7±6.4	156.7±6.7
Weight (kg)	57.4±9.4	54.3±7.9	57.0±9.3
BMI (kg/m^2)	23.2±3.6	23.3±3.0	23.2±3.5
Duration of RA (mo)	87.0±73.8	136.1±108.5	93.1±80.0
ACR functional class			
Class I	4 (3.8)	0 (0)	4 (3.3)
Class II	94 (88.7)	10 (66.7)	104 (86.0)
Class III	6 (5.7)	5 (33.3)	11 (9.1)
Class IV	2 (1.9)	0 (0.0)	2 (1.7)
DAS28-ESR score	-	-	5.5±0.8
BMD-T score*			
Lumbar region	-	-	−1.43±1.34
Femur region	-	-	−1.20±1.11†
ESR (mm/h)	-	-	42.4±22.5
CRP (mg/dL)	-	-	1.30±1.28
Bone turnover markers			
Bone-specific alkaline phosphatase			
Normal	-	-	81 (68.1)
Abnormal (non-significant)	-	-	35 (29.4)
Abnormal (clinically significant)	-	-	3 (2.5)
N (missing)	-	-	119 (2)
Osteocalcin			
Normal	-	-	94 (79.0)
Abnormal (non-significant)	-	-	25 (21.0)
Abnormal (clinically significant)	-	-	0 (0.0)
N (missing)	-	-	119 (2)
C-telopeptide			
Normal	-	-	117 (98.3)
Abnormal (non-significant)	-	-	2 (1.7)
Abnormal (clinically significant)	-	-	0 (0.0)
N (missing)	-	-	119 (2)
Receptor activator of NF-κB			
Normal	-	-	4 (100.0)
Abnormal (non-significant)	-	-	0 (0.0)
Abnormal (clinically significant)	-	-	0 (0.0)
N (missing)	-	-	4 (117)
Osteoprotegerin			
Normal	-	-	4 (100.0)
Abnormal (non-significant)	-	-	0 (0.0)
Abnormal (clinically significant)	-	-	0 (0.0)
N (missing)	-	-	4 (117)
Prior DMARDs/biological agents			
DMARDs	106 (100.0)	15 (100.0)	121 (100.0)
Methotrexate	97 (91.5)	14 (93.3)	111 (91.7)
Hydroxychloroquine	46 (43.3)	5 (33.3)	51 (42.1)
Sulfasalazine	41 (38.7)	5 (33.3)	46 (38.0)
Leflunomide	6 (5.7)	1 (6.7)	7 (5.8)
Others	12 (11.3)	3 (20.0)	15 (12.4)

Table 1. Continued

Characteristics	Patients aged ≤65 years (n=106)	Patients aged >65 years (n=15)	All patients (n=121)
Biological agents	3 (2.8)	1 (6.7)	4 (3.3)
Infliximab	2 (1.9)	0 (0.0)	2 (1.7)
Etanercept	0 (0.0)	0 (0.0)	0 (0.0)
Adalimub	1 (0.9)	1 (6.7)	2 (1.7)
Rituximab	0 (0.0)	0 (0.0)	0 (0.0)
RA medications other than DMARDs/biological agents	101 (95.3)	14 (93.3)	115 (95.0)

Values are presented as number (%) or mean±standard deviation unless otherwise stated. ITT: intention-to-treat, BMI: body mass index, RA: rheumatoid arthritis, ACR: American College of Rheumatology, DAS28: disease activity score in 28 joints, ESR: erythrocyte sedimentation rate, BMD: bone mineral density, CRP: C-reactive protein, NF-κB: nuclear factor κB, DMARD: disease-modifying anti-rheumatic drugs. *From screening visit. †n=120.

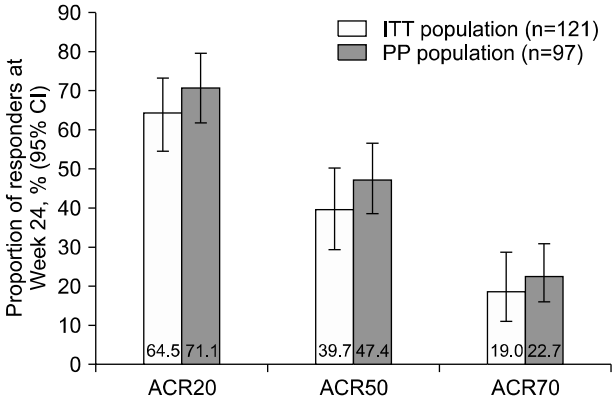

Figure 2. Proportion of ACR responders at Week 24 in the ITT and PP populations after 24 weeks of treatment with tacrolimus. ACR20, ≥20% improvement in the seven ACR response criteria. ACR50, ≥50% improvement in the seven ACR response criteria. ACR70, ≥70% improvement in the 7 ACR response criteria. ACR: American College of Rheumatology, ITT: intention-to-treat, PP: per-protocol, CI: confidence interval.

atitis B virus, and hepatitis C antibody levels that were either normal or not clinically significant. All patients had previously received DMARDs, other than tacrolimus. Overall, 3.3% of patients had received prior treatment with biological agents, and 95.0% were taking medication for RA other than DMARDs or biological agents (Table 1).

Twenty-five of the 124 enrolled patients were prematurely discontinued from the study. The most common reasons for discontinuation were withdrawal of consent (10/25 patients, 40.0%), AEs (7/25, 28.0%), low drug compliance (6/25, 24.0%), protocol violation (1/25, 4.0%), and other reasons judged by the investigator (1/25, 4.0%) (Figure 1).

Treatment

In the ITT population, patients received tacrolimus for a mean±SD of 154.5±42.5 and 134.3±57.2 days in the ≤65 and >65 years age groups, respectively, at an overall mean dose of 1.81±0.47 mg/day during the study.

At Week 12, a total of 12 patients (11.5%) aged ≤65 years were prescribed a 1 mg increase in tacrolimus daily dose, and two patients (1.9%) aged >65 years were prescribed a 0.5 mg increase in tacrolimus daily dose; no patient was prescribed a dose decrease. Most patients (90/104, 86.5%) were prescribed a consistent dosage of tacrolimus over the 24 weeks of treatment.

Throughout the study, the mean±SD compliance with tacrolimus therapy for the overall ITT population, and for patients aged ≤65 and >65 years was 90.7±18.9%, 91.7±18.3%, and 83.1±21.9%, respectively; 15 (12.4%), 11 (10.4%), and 4 (26.7%) patients had compliance <80%.

In the ≤65 and >65 years age groups, 4.7% and 6.7% of patients in the ITT population were receiving concomitant medication in addition to those they were receiving at screening (data not shown).

ACR response and DAS28-ESR

After 24 weeks of tacrolimus treatment, 78 patients (64.5%; 95% CI: 55.3%, 73.0%) in the ITT population were ACR20 responders, 48 patients (39.7%; 95% CI: 30.9%, 49.0%) were ACR50 responders, and 23 patients (19.0%; 95% CI: 12.5%, 27.1%) were ACR70 responders (Figure 2). A numerically higher proportion of patients were ACR20, ACR50, and ACR70 responders in the PP population compared with the ITT population (Figure 2).

In the ITT population, the mean±SD DAS28-ESR score decreased from 5.5±0.8 at baseline, to 3.7±1.5 after 24

weeks of tacrolimus administration ($p<0.0001$). A similar pattern was observed in the PP population (5.4±0.8 vs. 3.6±1.4 at baseline and Week 24, respectively; $p<0.0001$). The mean±SD change in DAS28-ESR score from baseline to Week 24 was −1.7±1.3 and −1.9±1.2 in the ITT and PP populations, respectively. At Week 24, the DAS28-ESR response EULAR classification was good or moderate for 78% of patients in the ITT population and for more than 80% of patients in the PP population (Table 2).

Table 2. DAS28-ESR response by EULAR classifications at Week 24, in the ITT and PP populations

EULAR classification (based on changes from baseline to Week 24)	ITT population (n=121)	PP population (n=97)
Good	42 (34.7) [26.3, 43.9]	38 (39.2) [29.4, 49.6]
Moderate	52 (43.0) [34.0, 52.3]	43 (44.3) [34.2, 54.8]
Non-response	27 (22.3) [15.3, 30.8]	16 (16.5) [9.7, 25.4]

Values are presented as number (%) [95% confidence interval]. DAS28: disease activity score in 28 joints, ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, ITT: intention-to-treat, PP: per-protocol.

BMD-T score and bone turnover markers

Between screening and Week 24 in the ITT population, there was no significant change in BMD-T score in the lumbar region (mean±SD change, −0.06±0.38; $p=0.1550$), or BMD-T score in the femur region (−0.04±0.28; $p=0.0936$), albeit that scores at screening and Week 24 both indicated osteopenia (Table 3). The pattern was similar in the PP population, although the decrease in BMD-T score in the femur region reached statistical significance ($p=0.0483$; Table 3). When the BMD-T score in the lumbar vertebra or femur region was classified according to the International Society for Clinical Densitometry, there was no significant change in classification between screening and Week 24, for the ITT or PP population (Table 3). There was also no significant difference between baseline and Week 24 in bone turnover marker levels in the ITT or PP population (data not shown).

Joint counts

In the ITT population, the mean±SD number of tender joints decreased by 7.7±9.1 between baseline and Week 24 (12.7±10.9 vs. 5.0±7.7, respectively), and the mean±SD number of swollen joints decreased by 4.1±4.2 (6.5±4.7 vs. 2.4±2.9, respectively). Results were similar in the PP population.

Table 3. Summary of BMD-T score at screening versus Week 24, and BMD-T score classification by ISCD guideline, for the ITT and PP populations

BMD-T score	ITT population	PP population
Lumbar vertebra region (n)	121	97
Screening	−1.43±1.34	−1.35±1.31
Week 24	−1.50±1.35	−1.42±1.34
Difference from screening to Week 24	−0.06±0.38	−0.06±0.33
p-value*	0.1550	0.1138
Transitioned from normal/osteopenia to osteoporosis (screening–Week 24)	2 (1.7)	1 (1.0)
Transitioned from osteoporosis to normal/osteopenia (screening–Week 24)	4 (3.3)	3 (3.1)
p-value†	0.6875	0.6250
Femur region (n)	120	96
Screening	−1.20±1.11	−1.10±1.10
Week 24	−1.24±1.08	−1.16±1.08
Difference from baseline to Week 24	−0.04±0.28	−0.06±0.26
p-value*	0.0936	0.0483
Transitioned from normal/osteopenia to osteoporosis (screening–Week 24)	2 (1.7)	1 (1.0)
Transitioned from osteoporosis to normal/osteopenia (screening–Week 24)	2 (1.7)	1 (1.0)
p-value†	1.000	1.000

Values are presented as mean±standard deviation or number (%) unless otherwise stated. BMD: bone mineral density, ISCD: International Society for Clinical Densitometry, ITT: intention-to-treat, PP: per-protocol. *Wilcoxon signed rank test. †McNemar's test.

VAS

All components of the VAS improved after 24 weeks of tacrolimus treatment. The mean±SD change in VAS score from baseline to Week 24 in the ITT population was −24.6±27.2 for pain, −19.1±27.1 for fatigue, −23.6±29.9 for patient-judged activity, and −24.8±23.4 for investigator-judged activity. Similar patterns were observed for the PP population.

Acute phase reactants

The mean±SD improvement in ESR was −12.5±19.7 mm/h between baseline and Week 24 (42.4±22.5 vs. 29.8±23.0 mm/h, respectively) for the ITT population. Overall, 32.2% of the ITT population transitioned from an abnormal ESR level at baseline to normal levels by Week 24, while 0.8% of patients transitioned from normal levels at baseline, to abnormal levels at Week 24.

The mean±SD improvement in CRP level was −0.54±1.39 mg/dL between baseline and Week 24 (1.30±1.28 vs. 0.77±1.11 mg/dL, respectively) for the ITT population. Overall, 41.3% of the ITT population transitioned from an abnormal CRP level at baseline to normal levels by Week 24, while 5.8% of patients transitioned from normal levels at baseline, to abnormal levels at Week 24. The changes in CRP levels and ESR between baseline and Week 24 were comparable in the ITT and PP population.

Safety

During 24 weeks of tacrolimus treatment, 56 patients (46.3%) experienced 93 AEs, most (75.3%) of which were mild in severity. Common AEs, reported in ≥1% of patients, are presented in Table 4; by system organ class, these were: gastrointestinal disorders (19.0% of patients, 23 events), infections and infestations (9.1%, 11 events), musculoskeletal and connective tissue disorders (5.8%, 7 events), and nervous system disorders (5.8%, 7 events). Five patients (4.1%) experienced serious AEs, one each of femur fracture, foot fracture, waist and wrist fracture, humerus fracture, and pneumonia. Three of the four fractures were caused by falling accidents. Only the foot fracture was identified as a treatment-related serious AE, without documentation for the specific cause of the fracture. The foot fracture and waist and wrist fracture led to study discontinuation.

Of the 93 reported AEs, 38 AEs (40.9%) were treatment-related, occurring in 25 patients (20.7%). The most commonly reported treatment-related AEs, by system organ class, were: gastrointestinal disorders (9.9% of patients, 12 events), infections and infestations (4.1%, 5 events), nervous system disorders (3.3%, 4 events), and renal and urinary disorders (2.5%, 3 events). Among the 25 patients with treatment-related AEs, 2 patients (1.7%) exhibited severe AEs, 11 (9.1%) discontinued the study due to the treatment-related AEs, and 1 (0.8%) experienced a treatment-related serious AE (fracture, described above). There were no patient deaths during the study.

Table 4. Incidence of AEs experienced by ≥1% of patients in the SAF, by system organ class and preferred term

AE term	SAF population (n=121)
Gastrointestinal disorders	23 (19.0)
Dyspepsia	7 (5.8)
Diarrhoea	4 (3.3)
Nausea	4 (3.3)
Constipation	3 (2.5)
Abdominal discomfort	2 (1.7)
Abdominal pain	2 (1.7)
Infections and infestations	11 (9.1)
Nasopharyngitis	7 (5.8)
Musculoskeletal and connective tissue disorders	7 (5.8)
Back pain	2 (1.7)
Musculoskeletal stiffness	2 (1.7)
Myalgia	2 (1.7)
Nervous system disorders	7 (5.8)
Dizziness	3 (2.5)
Tremor	3 (2.5)
Injury, poisoning and procedural complications	6 (5.0)
General disorders and administration site conditions	5 (4.1)
Fatigue	2 (1.7)
Renal and urinary disorders	4 (3.3)
Pollakisuria	2 (1.7)
Blood and lymphatic system disorders	3 (2.5)
Cardiac disorders	3 (2.5)
Palpitations	3 (2.5)
Respiratory, thoracic and mediastinal disorders	3 (2.5)
Cough	2 (1.7)
Productive cough	2 (1.7)
Skin and subcutaneous tissue disorders	3 (2.5)
Pruritus	2 (1.7)
Investigations	2 (1.7)
Haemoglobin decreased	2 (1.7)
Vascular disorders	2 (1.7)
Hypertension	2 (1.7)

Values are presented as number (%). AE: adverse event, SAF: safety-analysis set.

DISCUSSION

In this study, 24 weeks of per-protocol tacrolimus treatment in DMARD-resistant patients with RA resulted in a high proportion of ACR responders (64.5%, 39.7%, and 19.0% achieving an ACR20, ACR50, or ACR70 response, respectively). The mean DAS28-ESR score significantly improved from baseline to Week 24, and there were fewer tender or swollen joints. Furthermore, RA disease activity was reduced, and physical function was improved by Week 24. Tacrolimus therapy was generally well tolerated in this study, and the reported incidence of treatment-related AEs was low.

In this study, it is encouraging that the ACR20 response rate was 64.5%. This is higher than the ACR20 response rates reported in other tacrolimus studies, including those of patients receiving tacrolimus without concomitant DMARDs, in which the highest rates cited range between 48.3% and 52.5% [12,14,17-20]. ACR50 and ACR70 response rates in this study were also higher than those previously reported with tacrolimus therapy, with or without concomitant DMARDs [12,14,17-19,21]. This disparity between the high ACR response rates in our study and the lower rates previously described may be due to different patient characteristics, disease duration, or study design. For example, in a Phase II study with tacrolimus and without concomitant DMARDs that reported ACR20 and ACR50 response rates of 32.0% and 11.8%, respectively, patients had a longer duration of RA prior to study entry, and a greater proportion of patients with ACR functional class III disease, compared with our study population [21].

In this study, the mean DAS28-ESR score significantly decreased from baseline after 24 weeks of tacrolimus treatment, irrespective of study population. Furthermore, the DAS28-ESR response according to EULAR classification was good or moderate in 78% of patients at Week 24. Improvements in DAS28-ESR score have been reported in studies where tacrolimus has been used as an add-on therapy [12,22]. For example, a mean improvement from baseline to Week 16 in DAS28-ESR of −1.42 points was reported with lower-dose tacrolimus (1.5 mg) as add-on to methotrexate, in a Korean study of patients with active RA and an inadequate response to methotrexate [12]. Collectively, these data suggest that RA disease activity is effectively reduced following treatment with tacrolimus therapy.

RA is associated with osteoporosis [1], and tacrolimus has been shown to prevent differentiation of cells into mature osteoclasts [23], potentially reducing bone resorption. Consistent with this, in our study the mean BMD-T score in the lumbar region was similar at screening and Week 24, and there was no significant change from baseline to Week 24 in bone turnover marker levels. Worsening of the mean BMD-T score in the femur region between screening and Week 24 also failed to reach statistical significance in the ITT population. Furthermore, only two patients in the ITT population transitioned from BMD-T scores associated with normal bone density or osteopenia, to osteoporosis. However, due to lack of a control group that did not receive tacrolimus, the possibility of a spontaneous decrease in BMD over time in our population cannot be ruled out.

In both the ITT and PP populations, the mean number of tender and swollen joints decreased between baseline and Week 24 (by 7.7 and 4.1 in the ITT population, respectively). This is consistent with results from Furst et al. [18], who reported a mean reduction in tender and swollen joint count of −6.3 and −3.8, respectively, between baseline and Week 24, in patients who had received 3 mg tacrolimus after being treated unsuccessfully with methotrexate. Mean reductions in tender and swollen joint count were also comparable with those reported in other publications after 16 weeks of 1.5 mg tacrolimus therapy (−3.3 and −3.6, respectively) [19], 24 weeks of 2 mg tacrolimus therapy (−3.1 and −4.0) [21], and 28 weeks of 1.5 mg or 3 mg tacrolimus therapy (−7.1 and −4.1) [14].

Improvements in mean DAS28-ESR score, and reductions in the mean number of tender and swollen joints after initiating tacrolimus therapy, are likely associated with the largely positive patient perceived outcomes measured at Week 24. In both the ITT and PP populations, 24 weeks of tacrolimus therapy was associated with a reduction in pain and fatigue, and an increase in physical activity, as measured by VAS. A reduction in pain score on the VAS has also been reported in previous studies of tacrolimus in patients with RA [18,19], as have improvements in disease activity and patient health [21]. These data suggest that tacrolimus has the potential to improve quality of life for patients with RA, and their ability to perform daily activities, when treatment with DMARDs has been unsuccessful.

Importantly, there were no new safety concerns with tacrolimus therapy in this study. Consistent with Kawai and Yamamoto [14] and Kondo et al. [19], approximately half of patients in this study experienced AEs; however, most

AEs were mild in severity, and only 20.7% of patients experienced treatment-related AEs. The most common system organ class of AEs was gastrointestinal disorders, which is aligned with previous reports [18,21]. Overall, tacrolimus was well tolerated in patients with active RA and an unsuccessful response to DMARDs.

This study had several limitations, such as the lack of a comparator arm. It was also not possible to determine whether the efficacy of tacrolimus might decrease beyond 24 weeks of treatment. There was an insufficient number of patients to enable stratification of outcomes by the type of combination therapy used (eg., NSAIDs) and the planned study design did not include baseline assessment of laboratory values or NSAID/corticosteroid doses. Each centre's local laboratory measured the T-score, but not the absolute value of BMD. It should be noted, when making cross-study comparisons, that methods for BMD assessment may vary, and there was no calibration between the machines in each centre. Functional disability data were planned for inclusion, and determined using the Korean Health Assessment Questionnaire (KHAQ [24]) disability index; however, these data could not be included due to an error in the formula used throughout the study. Despite these limitations, the data generated by this study positively add to the growing pool of evidence for the use of tacrolimus to treat patients with active RA.

CONCLUSION

This study showed that 6 months of tacrolimus therapy (1.0 to 3.0 mg/day) diminished the RA activity, and improved the physical functions of joints in patients with active RA who were resistant to DMARDs in Korea, without clinically-meaningful deterioration in BMD. Overall, the incidence of treatment-related serious AEs and mild to moderate infections was low, and no unexpected safety signals were identified during the study period. Tacrolimus may, therefore, be a suitable therapy for patients with active RA who are resistant to DMARDs.

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CONFLICT OF INTEREST

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