ORIGINAL ARTICLES

Use of tacrolimus for managing csDMARD-failed rheumatoid arthritis: A real-time experience from a single tertiary care centre

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Abstract

Aim: To evaluate the efficacy of tacrolimus in achieving disease activity score-28-c-reactive protein 3 [DAS28-CRP (3)] remission in patients managed with tacrolimus at the end of 24 week in a tertiary setting.

Methodology: The retrospective study included RA patients who fulfilled American College of Rheumatology (ACR) 2010 criteria and managed by tacrolimus as an add-on to the background DMARD or as a substitute to conventional synthetic DMARD. Apart from demographic data, TJC, SJC, ESR and CRP were recorded at each visit. Subjects were grouped as those who achieved remission (DAS28-CRP (3) <2.6) and not under remission (DAS28-CRP (3)>2.6). Descriptive analysis was carried out for different variables in the classified groups, chi-square test for categorical variables and ANOVA and t-test to compare the continuous variables.

Results: The study selected 100 patients who fulfilled the criteria for analysis. The corresponding number of subjects who received 4 mg, 3 mg, 2 mg, 1.5 mg and 1 mg of tacrolimus were 3, 23, 57, 2 and 15 respectively. The corresponding number of patients evaluated at 3, 6, 9 and 12 months were 100, 86, 71 and 56. Around 20% of the patients reached a state of remission by the end of 12 months. The DAS28-CRP (3) remission (<2.6) was achieved in 7 (7%) out of 100 at the end of 3 months, which increased to 17 (20%) out of 86 by 6th month. Around 9 out of 57 maintained the remission till the end of 12 months and 11 (20%) out of 57, who were followed till 12th month, had moderate response. Discriminate function analysis showed that the age and duration of disease were strong predictors of achieving remission. Baseline DAS score and duration of illness at the time of introduction of tacrolimus negatively predicted the patients achieving remission.

Conclusion: Tacrolimus is beneficial to achieve remission by the end of 6 months in 20% of the patients with 3 or 4 DMARD-failure. It is also useful in patients who cannot use biologics.

Introduction

Tacrolimus, discovered in 1987, was coined from Tsukuba macrolide immunosuppressant.[1] It is a macrolide antibiotic originally isolated from *Streptomyces tsukubaensis*. It was first approved by the US Food and Drug Administration (FDA) in 1994 for renal transplant and later the use was expanded to the prophylaxis of transplant rejection (both adult and paediatric) of liver, and heart and kidney allograft recipients. In Japan, oral tacrolimus was approved for the treatment of RA in 2005 and topical tacrolimus for moderate to severe atopic dermatitis in 2002. Though there are adequate clinical trials and published studies, the drug is not approved for the management of RA in many countries including India. However, it is often used as an off-label indication in RA.[2] It is used by certain rheumatologists in patients with refractory RA and those intolerant to conventional synthetic DMARDs (csDMARDs), especially in circumstances where biologicals or other target synthetic DMARDs cannot be used.[3] Tacrolimus, being an immunomodulator, acts by inhibiting T-cell activation, preventing NF-kappa B activation by inhibiting the action of calcineurin, and regulating MMP-13 synthesis via

JNK pathway in rheumatoid synovium.[4-7] It has also been demonstrated to be effective by inhibiting P-glycoprotein (P-gp) function and expression in SLE, RA and PsA patients.[5] Measuring P-glycoprotein expression on lymphocytes can be a potentially useful marker for assessing response to tacrolimus in refractory RA.[8]

In the present tertiary care setting, tacrolimus is used as an off-label indication for managing RA. It is primarily used in scenarios where patients are not able to achieve low disease activity or not adequately responding or tolerating combination of csDMARD, and need to introduce biologic DMARDs or targeted synthetic DMARDs, however, they cannot be used either due to financial or medical reasons. The present retrospective study was designed to evaluate the efficacy of tacrolimus in achieving low disease activity or remission <2.6 and a good EULAR response at the end of 6 months in regular clinical care. Drugs safety as well the sustenance of the clinical remission till the end of 12th month were evaluated as secondary objective. The study also analyzed the factors that predict the response to tacrolimus.

Patients and methods

The retrospective observational study evaluated the efficacy and safety of tacrolimus for managing RA in a real-time scenario at a tertiary care centre. The patients who fulfilled the ACR 2010 criteria for diagnosis of RA and were managed by tacrolimus were included in the study. The selected subjects were those who had persisting RA activity, confirmed by DAS28-CRP (3) ≥3, despite adequate dose of csDMARD, and those who were prescribed with biologics treatment. The patients who could not receive biologics either because of economical or medical reasons were included. The study excluded patients who had DAS28-CRP (3) score <3, but tacrolimus was added to withdraw methotrexate or any other DMARDs due to pregnancy planning and/or adverse events, despite a good control. Patients with overlapping connective tissue diseases (CTD), osteoarthritis, and those with irregular follow-up and missing data were excluded. The study was approved by institutional ethical committee. The three drug combinations used were salazopyrin/leflunomide, methotrexate and hydroxychloroquine at maximum tolerable dose, and low-dose steroid (≤10 mg of prednisolone or equivalent drug).

The patient charts were reviewed for fulfilling criteria, and demographic data like age, gender, location and other vital characteristics were collected. The dosages of current DMARD and the add-on tacrolimus at each visit were noted. Details such as TJC, SJC, pain scale, inflammatory parameters like ESR and CRP, serum creatinine, CBC, change in blood pressure, creatinine levels and any adverse events were collected. DAS28-CRP (3) was calculated using the standard formula and the EULAR response was ascertained using the classification criteria.[9] Since the use of patient global assessment may yield inconsistent results in partially literate population, DAS 28-CRP(3) was considered in the current cohort. The patient's follow-up data at 6 months was taken as primary endpoint. Details of the patients who had completed subsequent follow-up till the end of 12th month, for adverse event as well disease activity were also retrieved. Tacrolimus was added to the background DMARD in certain patients and as a substitute to csDMARD in other subjects.

Statistical methods

DAS28-CRP (3) score was used to evaluate the effect of drug on the disease activity and the patients were grouped as those who achieved remission (DAS score <2.6) and not under remission (DAS score >2.6). The number of patients followed at baseline, 3rd, 6th, 9th and 12-month visits were analyzed. The patients were also grouped into good, moderate, and no response based on EULAR-DAS response criteria. Descriptive analysis was carried out for different variables in the classified groups. Chi-square test was used for categorical variables, and the ANOVA and t-test to compare the continuous variables. Responses of the two groups were also compared for 3rd and 6th month follow-ups. Percent change in DAS28-CRP (3) score from baseline to 3rd and 6th month follow-up was calculated and represented as comparative bar graphs. Odds ratio for all the variables was calculated and P value was determined with the help of Wald test. A linear regression analysis combination of age, duration of disease, CRP, SJC and TJC, NLR and base DAS28-CRP (3) score was used to evaluate discriminant analysis function to characterize the two classes of patients (under remission and no remission) who were on tacrolimus medication, and the outcomes were recorded at the 6th month. The factors predicting the remission at 6th month on tacrolimus were analysed and the group variables were compared by discriminant function analysis. Accuracy of prediction was measured in terms of specificity and sensitivity, and also represented using ROC graph. The cases that reported termination of treatment before 3 months were considered only for safety reporting.[11]

Results

A search of institution's database identified 145 patients who were initiated or treated with tacrolimus between 2018 and 2020. The study selected 100 patients who fulfilled the criteria for analysis. Nineteen patients were excluded due to missing of details pertaining to CRP, joint assessment or initial/follow-up visit, and 16 subjects with baseline DAS28-CRP (3) <3 and were advised to replace methotrexate with tacrolimus due to pregnancy or adverse effects. All patients were initiated with 0.5 mg of tacrolimus twice daily. Dose was escalated, every 2nd or 4th week, depending on the response, tolerability and serum creatinine levels. The corresponding number of subjects who received 4 mg, 3 mg, 2 mg, 1.5 mg and 1 mg of tacrolimus were 3, 23, 57, 2 and 15 respectively. The dose was stabilized by the end of 3rd or 6th month. In 69 patients, tacrolimus was added to previous triple- or double-drug treatment and in 5 patients, methotrexate was replaced with tacrolimus due to intolerance and dose of methotrexate was <10 mg per week. Leflunomide and hydroxychloroquine were replaced with tacrolimus in 21 and 2 patients respectively. Three patients discontinued tacrolimus between 3 and 6 months of treatment due to adverse events (1 each due to increased infection, hypersensitivity and excess of hair fall). Ten patients discontinued the treatment after 9 months with 3 mg of tacrolimus due to treatment failure. Dose was reduced from 3 to 2 mg in 2 patients due to infection, in 4 due to skin discoloration, and in 1 each due to itching and

Table 1: Baseline characteristics of the study population

Variables (n = 100)	Results
Age in years (mean)	50.43±10.50
Gender (M/F)	6 /94
Duration of illness when tacrolimus was added in months*	143.11±75.31
Duration of first symptoms at presentation in months*	66.69±66.10
Duration of follow up after starting tacrolimus in months*	67.82±66.73
RF (IU/ml)	83 (83%)
Anti-CCP (EU/ml)	14 (14%)
ANA	40 (40%)
Comorbidities	53%
TJC*	13.90±11.49
SJC*	4.75±4.96
CRP (mg/L) *	16.87±18.45
ESR (mm/hr) *	57.71±25.78
Single DMARD	11 (11%)
Double DMARD	59 (59%)
Triple DMARD	30 (30%)
Steroids	11 (11%)
Neutrophils (%) *	64.45±8.29
Lymphocyte (%) *	25.35±7.37
NLR ratio*	2.88±1.32
DAS*	4.82±1.61

*mean and standard deviation for all continues variable.
Number and percentage for categorical variables

Table 2: Dempgraphic comparsion between subjects with DAS score <2.6 and >2.6 at 6 months

Variables		6 months		
		<2.6	> 2.6	P-value
Age (years)		46.39±11.51	51.12±10.08	0.04#
Gender (M/F)		2 (15)	4 (65)	0.34$
Duration of illness when Tacrolimus was added		107.47±63.35	151.39±80.70	0.02#
Duration of follow up after Tacrolimus added		15.06±7.22	16.83±7.01	0.18#
ESR (mm/hr)		57.94±28.26	56.29±25.11	0.41#
Neutrophil (%)		64.05±10.44	64.13±7.91	0.49#
Lymphocytes (%)		26.74±9.78	25.47±6.91	0.27#
NLR ratio		3±2.10	2.79±1.11	0.29#
CRP (mg/L)		17.04±20.52	16.73±19.40	0.48#
TJC		6.82±7.90	15.61±11.57	0.00#
SJC		4.59±6.22	4.78±5.02	0.46#
DAS-B		4.01±0.93	5±1.16	0.00#
DAS-2		2.01±0.39	4.79±1.05	< 0.00001#
Single DMARD		1 (5.88%)	6 (8.70%)	0.04$
Double DMARDs		9 (52.94%)	44 (63.77%)	0.58*
Triple DMARDs		7 (41.18%)	19 (27.54%)	0.42*
0 Comorbidity		7 (41.18%)	34 (49.28%)	0.74*
1 Comorbidity		10 (58.82%)	23 (33.33%)	0.10*
2 Comorbidity		0	9 (13.04%)	0.00$
3 Comorbidity		0	2 (2.90%)	0.22$
4 Comorbidity		0	1 (1.45%)	0.47$
Steroids		1 (5.88%)	8 (11.59%)	0.01$
RF (76)	Positive (71)	16 (94.12%)	55 (79.71%)	0.3$
	Negative (5)	0	5 (7.25%)	
ANA (65)	Positive (33)	7 (41.18%)	26 (37.68%)	0.53$
	Negative (32)	6 (35.29%)	26 (37.68%)	

P-value*: Chi-square test, P-value$: Fisher exact test, P-value#: t-test

dry skin, reduced appetite, increased blood pressure and elevated creatinine.

The demographic details and baseline characteristics of 100 participants are briefed in table 1. The corresponding number of patients evaluated at 3rd and 6th month were 100 and 86. One patient discontinued tacrolimus due to adverse event prior to 6th month visit, whereas the other 13 visited the site even after the window period of 6 month. All 13 patients continued tacrolimus with almost similar proportion of response. The corresponding percentage of subjects who received single, double and triple DMARDs are listed below: Single DMARD- methotrexate (6%), leflunomide (7%); double DMARDs: methotrexate-hydroxychloroquine (36%), methotrexate-leflunomide (12%), leflunomide-hydroxychloroquine (11%); and triple DMARDs: methotrexate-hydroxychloroquine-leflunomide (28%). Dempgraphic comparsion between subjects with

DAS score <2.6 and >2.6 at 6 months is provided in table 2.

The DAS28-CRP (3) remission (<2.6) was achieved in 7 (7%) out of 100 patients at the end of 3 months, which increased to 17 (20%) out of 86 subjects by 6th month (Fig. 1). Whereas, 19 out of 100 patients had moderate EULAR response at the end of 3rd month, and 15 out of 86 at the end of 6th month. Around 9 out of 57 patients acheived the state of remission (DAS 28 (3) CRP <2.6 by the end of 12th month and 11 (20%) out of 56, who were followed till 12th month, had moderate response (Fig. 2, 3 and 4).

Among 57 patients who were followed up during all the 4 visits, 9 had sustained remission till their 12th month follow-up. Lower duration of illness following the introduction of tacrolimus, and lower baseline DAS score, TJC and age were appeared to favour remission. Discriminate function analysis showed that the age and duration of disease were strong predictors of achieving remission. Baseline DAS score and duration of illness at the time of introduction of tacrolimus negatively predicted the patient's achieving remission.

None of the patients who had undergone methotrexate replacement attained remission within 12 months of follow-up. In the patient group where leflunomide was replaced with tacrolimus, the corresponding number of patients who attained remission at 3rd, 6th, 9th and 12th months out of 21 subjects were 1, 4, 4 and 2 respectively. The results were more favorable when tacrolimus was added to the existing triple drug combination (Table 3).

Discussion

The current study showed that the use of tacrolimus in nearly 20% of the patients who were either resistant or intolerant to methotrexate, hydroxychloroquine in combination with leflunomide or sulfasalazine assisted in attaining remission by the end of 6 months. Moreover, the same proportion of patients had moderate response with a significant reduction in overall DAS score. However, 6 out of 100 patients discontinued the treatment of tacrolimus because of adverse events and none of them had any serious adverse events.

Sixteen patients received tacrolimus when DAS score was <2.6 and they were subjects planning for pregnancy, those who could not afford biologics and unable to discontinue methotrexate and needed a replacement DMARD. Considering the safety profile of tacrolimus in pregnancy, the drug was added to patients who had inadequate control or intolerance to sulfasalazine or hydroxychloroquine. The primary objective was to assess the achievement of LDA/remission (DAS <2.6), rather than just improvement. In contrast to traditional inclusion criteria of ≥3.6, the present study used a cut-off of >3, where a substitute or add-on DMARD was suggested to achieve the treat to target.[12]

In concurrence with the present study findings, a study by Aramaki *et al.* noted that 23 of 106 patients (21.7%) treated with tacrolimus achieved DAS28-CRP remission at 6 months. Among the study participants, only 20 subjects were on methotrexate (18.9%), and majority were on prednisolone (93, 87.7%). The logistic regression analysis showed that male gender and moderate disease activity at baseline are independent predictors of achieving DAS28-CRP remission at 6 months.[13] However, majority of the current patients had reported failure of >3 DMARDs and the duration of illness upon initiation of tacrolimus was more as opposed to Kawakami *et al.* Similar study by Ishida et al. reported slightly higher proportion of subjects attaining (33.3%) remission at the end of 6 months.[14]

A study by Suzuki *et al.* noted that patients who received tacrolimus as monotherapy at dose 1, 2 or 3 mg once daily had the following moderate or good response rates: 38.2% (4 weeks), 41.8% (12 weeks), and 45.6% (24 weeks).[4] Kanzaki et al. demonstrated that tacrolimus in combination with MTX is safe and conferred long-term benefits.[5] The reduced EULAR response noted in the current study could be due to the inclusion of subjects who had >3 DMARD failure. The median DAS28-CRP (3) was reduced significantly in subjects who received tacrolimus with methotrexate in comparison to the control group.[6] Moreover, the addition of tacrolimus to DMARDs significantly suppressed the disease activity and joint destruction in patients with early rheumatoid arthritis (disease duration ≤3 years, CRP <1.5 mg/dL) who experienced poor response to oral DMARDs.[7] A similar retrospective study by Motomura et al. reported good or moderate response of 63%, 63%, 74% and 69% in patients followed up at 3, 6, 12, and 24 months, respectively and 47% and 50% had reached low disease activity or remission reached at 12 and 24 months respectively. The study has concluded that tacrolimus in real clinical practice could be beneficial in attaining good overall survival rate in patients with RA.[8] Tacrolimus improved disease activity in methotrexate-resistant or -intolerant patients with RA. A dose response with efficacy and toxicity indicated optimal dose to be >1 mg and≤3 mg daily.[15] The current study has

Fig.1: Proportion of patients with moderate EULAR response criteria at different time intervals

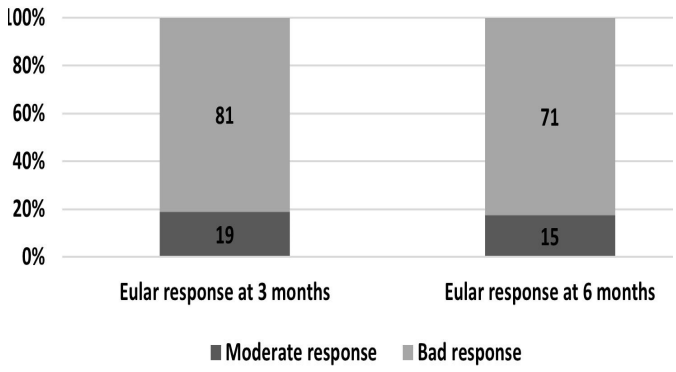

Fig. 2: Cumulative change in DAS 28 (3) CRP at 3rd and 6th months

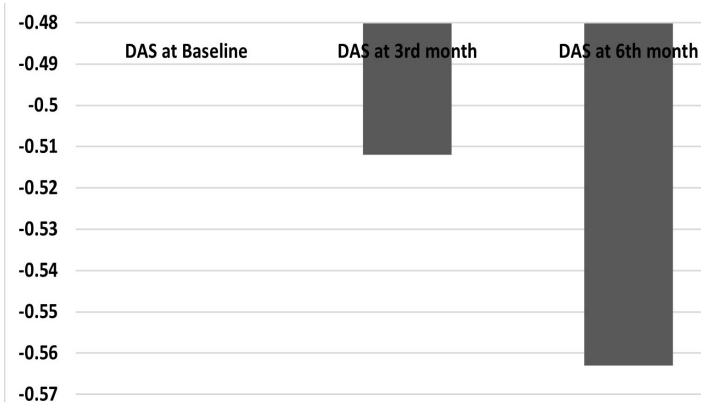

Fig. 3: Proportion of patients who achieved DAS 28 (3) CRP <2.6

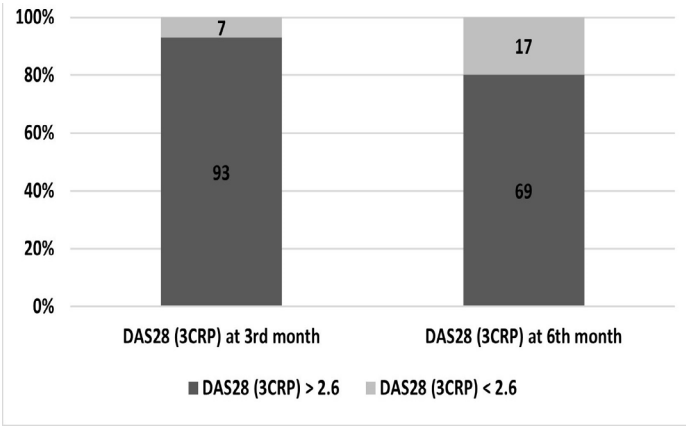

Fig. 4: Attainment and maintenance of DAS28 (3CRP) < 2.6

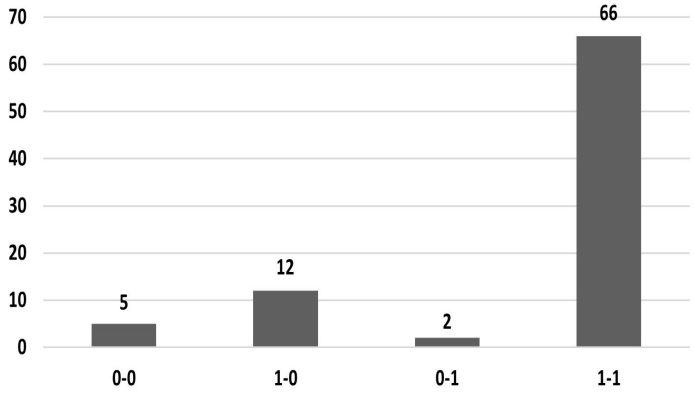

Table 3: Number of patients in remission who received combination therapy at baseline and after replacing the drugs with tacrolimus

Drugs used at baseline before tacrolimus replacement (n)	3 months (7/100)$	6 months (17/86)$	9 months (15/71)$	12 months (9/56)$
Mtx (6)*	**0**	**0**	**1**	**1**
Lef (6)*	1	1	1	1
Mtx+HCQ (36)*	2	5	5	2
Mtx+Lef (11)*	0	0	2	1
Lef+HCQ (11)*	1	4	5	3
Drugs replaced with tacrolimus				
Mtx (5)#	**0**	**0**	**0**	**0**
Lef (21)#	1	4	4	2
HCQ (2)#	**0**	**0**	**0**	**0**

*Mtx: methotrexate, HCQ: hydroxychloroquine, Lef- leflunomide. *number in each group, # number where tacrolimus replaced the drug mentioned, $ number of patient in remission/no followed at that point

corroborated the efficacy of tacrolimus dosage between 1 mg to 3 mg.

A multi-centre open-label study conducted at 13 US sites in patients who had active RA, despite treatment with maximally tolerated dosage of oral MTX, concluded that tacrolimus-MTX combination is safe and well-tolerated. The ACR20 clinical response attained at the end of treatment in patients who received 3 mg/day of tacrolimus was 52.5%. The corresponding number of patients who withdrew following adverse events and lack of efficacy were 7 (12.5%) and 4 (5.0%). In the present study, 6 out of 100 withdrew due to adverse events. In the US study, one patient had pancreatitis.[16] The long-term study has proven the safety and efficacy of tacrolimus in a significant proportion of patients to maintain the response.[16] The TREASURE study by Dong Hyuk Sheen *et al.* demonstrated the effectiveness and safety of 6-month tacrolimus therapy in patients with active RA and inadequate response to DMARDs and a major proportion of the subjects showed improved DAS28-ESR score and physical joint function.[17]

The aforementioned study in comparison to the present study had significantly higher percentage of response. The lesser response noted in the current cohort could be explained by the fact that majority of the patients were treated with triple DMARD and had failed to this combination. Yocum *et al.* observed that subjects who had DMARD-intolerance had better ACR response than DMARD-resistant patients.[18] A meta-analysis involving 1014 DMARD-resistant or -intolerant patients with a median follow-up duration of 6 (range 4-6) months concluded that tacrolimus at a dosages of 1.5-3 mg/day is effective in both DMARD-resistant and -intolerant patients with active RA.[16] Several studies have concluded on the usefulness and economic benefits of tacrolimus in managing RA in patients who are unable to use biologic agents.[20,21]

In addition, tacrolimus can be used as an add-on to RA patients with inadequate response to methotrexate+TNF inhibitors and abatacept-methotrexate combination.[21-24] The combination of methotrexate and tacrolimus had equal response and was non-inferior to leflunomide and methotrexate.[25] Adverse events reported were minor and gastrointestinal symptoms were common and did not cause any serious safety problems.[26] Neurotoxic adverse effects, including myoclonus, have been reported to be rare.[27] In the present cohort, treatment was discontinued in one patient due to the occurrence of tremors .

The discriminant function analysis indicated that higher disease activity and longer disease duration were the negative predictors of response to tacrolimus. This is in concurrence with the findings of Park *et al.* who reported baseline high disease activity as a significant risk factor for tacrolimus discontinuation after adjusting for confounding factors. Discontinuation of the treatment was due to inefficiency.[28] In the present study, higher CRP and tender joint counts favoured the outcome.

Major limitations of the study were single centre design and retrospective nature. The number of patients was adequate, with the possibility of 10% reaching remission. The study had adequate power based on the current sample size (80%).[29] One of the primary objectives was to estimate the proportion of patient who had achieved the treat-to-target remission, and the study had validated the potential of tacrolimus to be an alternative candidate. However, the background drugs were not uniform and their effects on response could not be ascertained, since the number of patients was small in each group. The preliminary analysis showed it to be a non-significant factor influencing the outcome. The annual cost of tacrolimus around 40,000/ INR, whereas biologic therapy costs around 1,00,000/ INR per annum. Considering the cost saving and with fair proportion of patients achieving the treat to target safely, a comparative study of tacrolimus with biologics is warranted to corroborate this observation, but the feasibility of such trial is comparatively low.

In conclusion, tacrolimus is a useful drug for managing RA and it can help to achieve remission in a good proportion of patients, even in scenarios with 3 to 4 DMARD failure. It can be a good alternative in patients who cannot use biologics due to medical and economic reasons.

Competing interests
The authors declare that they have no competing interests.

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