Clinical efficacy of tacrolimus in systemic lupus erythematosus with various manifestations: a real-world study

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To the Editor: Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple systems. In recent years, the therapeutic treat-to-target (T2T) strategy was recommended for SLE.[1] The immunosuppressive drugs are the standard of care in SLE treatment. Tacrolimus was one of the calcineurin inhibitors which was recommended in the 2019 update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association recommendations for the management of lupus nephritis (LN).[2] However, few studies have focused on tacrolimus for the management of various extra-renal SLE manifestations [Supplementary Table 1, http://links.lww.com/CM9/B122]. There are also no T2T data about tacrolimus in SLE. So, we conducted this single-center, prospective, real-world study to better clarify the efficacy and safety of tacrolimus in various SLE manifestations and provide T2T evidence for tacrolimus.

Based on the Chinese SLE Treatment and Research group registry,[3] SLE patients who fulfill the 2012 Systemic Lupus International Collaborating Clinics classification criteria and with a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) ≥2 were included from March 2016 to March 2020 in Peking Union Medical College Hospital. The main exclusion criteria included patients diagnosed as neuropsychiatric lupus, pregnancy, and undergoing steroid pulse therapy or the addition of other immunosuppressants except for tacrolimus at baseline. This study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital (Nos. S-478 and JS-2038).

Baseline information included demographics, SLE duration, clinical manifestations, laboratory parameters, current medications, and disease activity. Patients were treated with tacrolimus and followed up at 3 months or 6 months. Disease activity was assessed using the Physician Global Assessment (PGA) and SLEDAI-2K scores. Lupus Low Disease Activity State (LLDAS)[4] was defined as (1) SLEDAI-2K ≤4, with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity; (2) no new lupus disease activity compared with the previous assessment; (3) PGA ≤1; and (4) prednisolone (or equivalent) ≤7.5 mg daily. According to the European consensus criteria, SLE remission was defined as a clinical SLEDAI-2K = 0 and PGA <0.5, with prednisolone (or equivalent) ≤5 mg daily. The complete remission (CR) of thrombocytopenia was defined as platelet count $\geq 100 \times 10^9$/L, and partial remission (PR) was defined as platelet count $\geq 30 \times 10^9$/L and at least a two-fold increase from baseline. CR of LN was defined as 24-hour urine protein (24 hUPro) ≤0.5 g/24 h, inactive urinary sediment, and serum creatine returned to normal, and PR was defined as a 50% reduction in 24 hUPro, urine protein <3.5 g/24 h, and serum creatine within 25% of the baseline value. Pulmonary arterial hypertension (PAH) was defined as a resting mean pulmonary artery pressure >25 mmHg assessed by right heart catheterization, in the presence of normal pulmonary capillary wedge pressure <15 mmHg and pulmonary vascular resistance >3 Wood units, or a resting systolic pulmonary artery pressure >40 mmHg estimated by transthoracic echocardiography. The primary endpoint was the SLEDAI-2K. Secondary endpoints included PGA, remission or LLDAS, serum complement level and titer of the anti-dsDNA antibody, glucocorticoids dose, and remissions of organ involvement.

The paired samples *t* test or Wilcoxon signed-rank test was used to compare continuous variables, while the chi-square test or Fisher's exact test to compare categorical variables, where appropriate. Two-tailed $P < 0.05$ was considered

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statistically significant. Analyses were performed using SPSS 21.0.0.0 (IBM Corp., Armonk, NY, USA).

A total of 96 patients were included [Supplementary Figure 1, http://links.lww.com/CM9/B122]. The average age was 33.0 ± 9.3 years old, while the average duration of SLE was 6.8 ± 5.6 years. Five SLE manifestations were included in our study: mucocutaneous involvement (6/96, 6.3%), arthritis (4/96, 4.2%), hematologic disorder (30/96, 31.3%), LN (65/96, 72.1%), and PAH (28/96, 29.2%). The average initial dosage of tacrolimus was 2.1 ± 0.5 mg/day. Tacrolimus was prescribed alone in 77 (80.2%) patients, including those prescribed as first-line immunosuppressants with no previous immunosuppressants in 53 (55.2%) patients, and switched from other immunosuppressants in the other 24 (25.0%) patients. In the remaining 19 (19.8%) patients, tacrolimus was added on without suspending previous immunosuppressants [Supplementary Table 2, http://links.lww.com/CM9/B122]. Tacrolimus was stopped, switched to, or combined with other immunosuppressants within 3 months in six patients because of inferior effects or adverse events. The remaining 90 patients with 3 months or 6 months of follow-up data of tacrolimus treatment and whose dose of concomitant immunosuppressants was not changed during follow-up were enrolled for further analyses of the efficacy of tacrolimus.

After tacrolimus treatment, the SLEDAI-2K score decreased significantly (5.7 ± 3.5, 3.2 ± 3.1, and 2.8 ± 2.4 at baseline and at months 3 and 6 visits, respectively; $P < 0.001$ and $P < 0.001$ compared with baseline, respectively; Supplementary Figure 2A, http://links.lww.com/CM9/B122), as did the PGA (0.76 ± 0.49, 0.50 ± 0.41, and 0.43 ± 0.35 at baseline and at months 3 and 6 visits, respectively; $P < 0.001$, and $P < 0.01$ compared with baseline, respectively; Supplementary Figure 2B, http://links.lww.com/CM9/B122). Compared with baseline, the prednisone dosage reduced after tacrolimus treatment (21.8 ± 18.2 mg/day, 13.9 ± 8.4 mg/day, 10.2 ± 5.5 mg/day at baseline and at months 3 and 6 visits, respectively; $P < 0.001$ and $P < 0.001$ compared with baseline, respectively; Supplementary Figure 2C, http://links.lww.com/CM9/B122). Among the 54 patients with 6 months of follow-up data, 22 (40.7%) achieved remission or LLDAS at 6 months (Supplementary Figure 2D, http://links.lww.com/CM9/B122). Both complement C3 (0.757 ± 0.237 g/L, 0.849 ± 0.257 g/L, and 0.857 ± 0.255 g/L at baseline and at months 3 and 6 visits, respectively; $P < 0.001$ and $P < 0.01$ compared with baseline, respectively; Supplementary Figure 2E, http://links.lww.com/CM9/B122) and C4 (0.130 ± 0.066 g/L, 0.151 ± 0.075 g/L, and 0.141 ± 0.059 g/L at baseline and at months 3 and 6 visits, respectively; $P < 0.01$ and $P < 0.01$ compared with baseline, respectively; Supplementary Figure 2F, http://links.lww.com/CM9/B122) level increased significantly. The anti-dsDNA antibody titer decreased significantly (359 ± 236 IU/mL, 270 ± 292 IU/mL, and 215 ± 219 IU/mL at baseline and at months 3 and 6 visits, respectively; $P < 0.001$ and $P < 0.01$ compared with baseline, respectively; Supplementary Figure 2G, http://links.lww.com/CM9/B122).

Regarding organ remission, 66.7% (4/6) patients with skin rash and 50.0% (2/4) patients with arthritis were relieved. 44.4% (4/9) of patients with thrombocytopenia who had follow-up data achieved CR by 6 months. 52.0% (13/25) of LN patients with baseline 24 hUPro ≥0.5 g achieved renal remission (eight CR and five PR) by 6 months. The 24 hUPro also improved significantly (1.97 ± 1.55 g/24 h, 1.04 ± 0.98 g/24 h, and 0.64 ± 0.43 g/24 h at baseline and at months 3 and 6 visits, respectively; $P < 0.05$ and $P < 0.01$ compared with baseline, respectively; Supplementary Figure 2H, http://links.lww.com/CM9/B122). Among the 28 patients with PAH, 18 (64.3%) patients were diagnosed as PAH by right heart catheterization, while the other 10 (35.7%) patients only by transthoracic echocardiography [Supplementary Table 3, http://links.lww.com/CM9/B122]. In addition to steroids and immunosuppressants therapy, 22 (78.6%) of the 28 patients with SLE-PAH were treated with PAH-specific vasodilator therapy. Twenty-six patients with PAH were followed up regularly with no changes in immunosuppressants and PAH-specific vasodilator therapy. The SLEDAI-2K (4.6 ± 3.4, 2.6 ± 3.5, and 2.2 ± 2.6 at baseline and at months 3 and 6 visits, respectively; $P < 0.01$ and $P < 0.05$ compared with baseline, respectively) of patients with SLE-PAH was improved after tacrolimus treatment. The proportion of the World Health Organization functional class I or II (19 [73%] of 26 patients at baseline and 16 [100%] of 16 patients at 6 months, respectively; $P < 0.05$) was improved. The N-terminal pro-brain natriuretic peptide (NT-proBNP) level (571 ± 632 pg/mL, 721 ± 1184 pg/mL, and 189 ± 226 pg/mL at baseline and at months 3 and 6 visits, respectively; $P = 0.133$ and $P = 0.198$ compared with baseline, respectively) appeared to be decreased but with no statistical difference.

Adverse events during tacrolimus treatment were observed in nine (9.4%) cases over 6 months. The most common adverse event was elevated serum creatine (4/96, 4.2%), followed by headache, hypertension, infection, gastrointestinal symptoms, and elevated liver enzymes in one patient each (1/96, 1%). Drug discontinuation within 3 months occurred in six patients due to inferior effects ($N = 3$), headache ($N = 1$), elevated serum creatine ($N = 1$), and unknown reason ($N = 1$).

This is the first and largest prospective real-world study to evaluate the efficacy of tacrolimus in SLE with various manifestations. Consistent with other studies [Supplementary Table 1, http://links.lww.com/CM9/B122], not only a significant improvement in SLEDAI-2K score and serological activity, but also the remission of various SLE manifestations such as LN, arthritis, skin rash, and thrombocytopenia were prominent in our study after tacrolimus treatment.

Unique to our study, we found that tacrolimus might be a therapeutic choice of immunosuppressants in SLE-PAH. The high percentage of PAH patients involved to our study might due to our hospital was a referral center of SLE-PAH. Tacrolimus already had some evidence in other PAH researches according to the mechanism of activation of bone morphogenetic protein receptor 2 signal pathway.[5] However, there is no evidence of tacrolimus for SLE-PAH before. According to our study, tacrolimus combined with or without vasodilator therapy might improve not only the

SLEDAI-2K score but also the heart function of patients with SLE-PAH. Further research should be conducted to clarify the efficacy and safety of tacrolimus in SLE-PAH.

This is also the first study to provide T2T evidence of tacrolimus treatment in SLE. In recent years, SLE remission or low disease activity was thought to be an achievable and desirable therapeutic target in SLE and is associated with benefits in decreasing organ damage in SLE.[4] We found that more patients achieved remission or LLDAS at 6 months after tacrolimus treatment.

In conclusion, we found that tacrolimus was effective in patients with active SLE with various manifestations and might help patients with SLE to achieve LLDAS in this real-world study. Tacrolimus might be helpful in SLE-PAH, which has not been investigated previously. Further high-quality randomized clinical trials and prolonged follow-up duration are required to demonstrate the efficacy and safety of tacrolimus in SLE.

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Conflicts of interest

None.

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