Long-term safety and effectiveness of tacrolimus in lupus nephritis patients: 5-year interim post-marketing surveillance study in Japan (TRUST)

Authors: Tsutomu Takeuchi MD, PhD[1] [https://orcid.org/0000-0003-1111-8218], Naoko Wakasugi, MSc[2] [https://orcid.org/0000-0002-9671-7174], Satoshi Uno, MSc[2], Hirofumi Makino MD, PhD[3] [https://orcid.org/0000-0002-1559-3799]

MeSH terms: lupus nephritis, immunosuppressive agent, post-marketing product surveillance

Affiliations:

[1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-Ku, Tokyo 156-0044, Japan

[2]Astellas Pharma Inc., 2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan

[3]Okayama University, 700-8530 1-1-1 Tsushimanaka, Kita-Ku, Okayama-Shi, Japan

Funding sources: This work was supported by Astellas Pharma, Inc. Editorial support was funded by Astellas Pharma, Inc.

Conflict of interest statement: All authors report non-financial support from Astellas during the development of the manuscript. NW and SU are employees of Astellas.

Authorship: All authors were involved in the study design and data interpretation; T Takeuchi and H Makino collected the data. All authors critically reviewed and approved the content of the manuscript.

Corresponding author:

Naoko Wakasugi

Astellas Pharma Inc., 2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan

Phone: 81-3-3244-0486

Fax: 81-3-3243-5727

Email: naoko.wakasugi@astellas.com

Short running head (max 4 words): Tacrolimus for lupus nephritis

ABSTRACT

Objective

To assess the long-term safety and effectiveness of tacrolimus for treating lupus nephritis (LN) in the real-world clinical setting.

Methods

This is an ongoing, open-label, non-comparative, observational, post-marketing surveillance study conducted across 275 sites in Japan. Registered LN patients are being followed for 10 years. Here we report data relating to 5 years of tacrolimus maintenance therapy at the interim data cutoff in August 2016.

Results

Of 1395 registered patients, 1355 received tacrolimus maintenance therapy for LN and provided safety data. The most common serious adverse drug reactions (ADRs) included pneumonia (1.1%), herpes zoster (1.0%), cellulitis (1.0%) and diabetes mellitus (1.0%). ADRs occurred mainly within the first 28 weeks of tacrolimus treatment, and no marked increase was observed during the follow-up period. Subgroup analyses suggested that risk factors for commonly observed ADRs associated with tacrolimus included inpatient management, LN disease severity,

increasing age, abnormal renal or hepatic function, and comorbid or previous disease. The cumulative rate of progression to renal failure (based on the attending physician's assessment) was 0.8% at Year 1, and 6.6% at Year 5. Cumulative relapse rates were 7.8% and 30.6%, respectively. Urine protein:creatinine ratio, serum anti-dsDNA antibody levels, complement C3 levels, and steroid-sparing effect were all significantly improved from 4 weeks after tacrolimus treatment initiation ($p<0.001$), and were sustained over 5 years.

Conclusion

Long-term tacrolimus maintenance treatment over 5 years in the real-world clinical setting was well tolerated and effective in a large population of patients with LN.

[Clinical trial registration number (www.ClinicalTrials.gov): NCT01410747]

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with wide-reaching effects on most organ systems, including the kidneys. Approximately 40–70% of patients with SLE will develop lupus nephritis (LN) (1), which is associated with substantial patient morbidity and mortality, particularly in certain populations, such as Afro-Americans and Asians (2–5).

The pathogenesis of LN is highly complex, and believed to be closely related with both systemic and intra-renal events (6–9). Genetic predisposition, proinflammatory and anti-inflammatory cytokines, as well as defects in the complement system all have putative roles in the development of LN. In addition to these pathogenic factors, the role of autoantibodies, such as anti-double-stranded DNA (dsDNA) antibody and aberrations in lymphocyte subsets, cannot be over-emphasized in the pathogenesis of LN, and are amenable to immunosuppressive treatments (5). Aberration of T lymphocytes, especially the T-helper (Th) subsets, including Th1, Th2, Th9, Th17, regulatory T cells and follicular Th cells, as well as B lymphocyte aberration are reported to play a crucial role in the pathogenesis of LN (5).

The treatment of LN mainly involves remission induction therapy in the acute stage followed by maintenance therapy (10). Cytotoxic agents, such as cyclophosphamide, in combination with corticosteroids, are the standard of care for LN treatment, but are associated with considerable morbidity and suboptimal outcomes (11). Immunosuppressants, such as azathioprine, mycophenolate mofetil and ciclosporin, can also be used to achieve better control of disease activity, with corticosteroid use as the basis of all regimens (12), but these therapies are associated with efficacy and safety concerns and a lack of supporting evidence (12).

Tacrolimus, an immunosuppressive macrolide that blocks T cell activation by specifically inhibiting calcineurin, is widely administered following organ transplantation (13). Tacrolimus therapy is considered as a promising treatment option for LN due to associated improvements in the aberrational activation of T lymphocytes, especially Th subsets in LN. Following several randomized studies evaluating the efficacy and safety of tacrolimus as maintenance treatment for LN (14,15), tacrolimus was approved for LN treatment in Japan in 2007, and subsequently in other Asian countries. However, data concerning the long-term safety and effectiveness of tacrolimus in LN patients in the real-world clinical setting are lacking. This post-marketing surveillance (PMS) study was undertaken in Japan

to assess the long-term safety and effectiveness of tacrolimus for maintenance treatment of LN in the real-world clinical setting. Patients are being followed for up to 10 years. Here we report the interim results of a 5-year analysis, involving 1355 registered patients.

MATERIALS and METHODS

Study design

A Study to Evaluate the Safety and Efficacy of Tacrolimus for Lupus Nephritis Under Actual Use Situations (TRUST; ClinicalTrials.gov: NCT01410747) is an open-label, non-comparative, non-interventional, observational, PMS study. TRUST was designed to prospectively assess the long-term safety and effectiveness of tacrolimus as maintenance therapy for LN in the real-world clinical setting, and aimed to include all sites in Japan with the potential to prescribe tacrolimus for LN. Ultimately, patients with LN initiating maintenance treatment with tacrolimus at 275 hospitals and clinics across Japan were registered centrally in an all-patient investigation system between January 2007 and January 2010. Registered patients are being followed for 10 years, with planned safety and effectiveness evaluations at 4, 8, 12 and 28 weeks; 1, 1.5 and 2 years, and annually thereafter. Here we report

safety and effectiveness data relating to 5 years of tacrolimus maintenance therapy at the interim data cutoff in August 2016.

Patients

Patients with LN were initiated with tacrolimus (Prograf®, Astellas Pharma Inc.) therapy at an individualized dose, and were then maintained on tacrolimus. The dose of tacrolimus during maintenance therapy could be adjusted for each patient on the basis of clinical signs and symptoms, aided by monitoring of tacrolimus blood trough concentrations (determined according to local standard practice). Prednisolone use was permitted at the discretion of the treating physician.

Study assessments

Adverse events (AEs) occurring during 5-year treatment with tacrolimus were monitored. Particular attention was paid to the occurrence (based on the attending physician's assessment) of infections, renal disorders, glucose tolerance disorders, neuropsychiatric disorders, cardiac disorders, pancreatic dysfunction, malignancy (including lymphoma), worsened interstitial pneumonia and menstrual disorders, which are identified as safety concerns of tacrolimus treatment.

Terminology of the Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J; version 19.0) was used to summarize and report AEs and ADRs according to system organ class and preferred terms. Renal and hepatic impairment and cardiac dysfunction were defined in the study protocol (see **Supplementary Appendix 1**), and formed the basis for the physician's rating of renal, hepatic or cardiac function as normal or abnormal. Adverse drug reactions (ADRs) were defined as AEs having at least a possible relationship to the study drug as assessed by the physician or for which assessment of causality was missing. An ADR was considered serious if it resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity.

Effectiveness variables

Variables used to assess the effectiveness of tacrolimus maintenance therapy included cumulative rates of progression to renal failure, dialysis and relapse (based on the attending physician's assessment according to local standard clinical practice); changes in urine protein:creatinine ratio (UPCR); serum anti-dsDNA antibody levels, serum complement C3 levels; and change in concomitant prednisone dose from baseline.

Statistical analyses

Categorical variables are shown as n (%) and continuous variables as mean ± standard deviation (SD). The tacrolimus continuation rate and cumulative incidence rates of ADRs over the 5-year follow-up were calculated by survival analysis using the Kaplan–Meier method. Subgroup analyses were performed to identify factors affecting the incidence of selected ADRs (including infections, renal disorders and glucose tolerance disorders) using Fisher's exact test (two subgroups) or the Cochran–Armitage trend test (three or more subgroups). The log-rank and generalized Wilcoxon tests were performed to compare survival curves and in the analysis of renal prognosis. Changes in effectiveness variables from baseline at each evaluated time point were analyzed using the Wilcoxon signed-rank test. Subgroup analyses were also performed to assess factors affecting rates of progression to renal failure, dialysis and relapse.

All statistical comparisons were performed using two-sided tests at the 0.05 significance level. No analyses were performed to adjust for type I error associated with multiple hypothesis testing. Missing data were not imputed in any of the analyses. In the survival assessment, patients who dropped out or were lost to

follow-up without events of interest were censored at subsequent assessments. All analyses were performed using SAS® (version 9.4).

Ethics

The study protocol (**Supplementary Appendix 1**) and amendments were submitted to the Ministry of Health, Labour and Welfare (MHLW). A written agreement was obtained from participating institutions. The study was performed in accordance with the standards for Good Post Marketing Study Practice (GPSP) provided by the MHLW in Japan. As GPSP is the authorized standard for PMS studies of approved drugs in clinical practice, no formal ethics committee approval was necessary, and informed consent was not required. To maintain privacy, all patient data were anonymized.

RESULTS

Patients

Patient disposition is presented in **Supplementary Figure 1**. Case report forms were collected for a total of 1395 LN patients. In all, 51.5% of patients were treated at university hospitals, 20.7% at government hospitals, 14.8% at public hospitals, 4.6% at national hospitals, and 11.6% at general hospitals or clinics. Most patients were treated in rheumatology departments (67.8%), followed by nephrology departments (28.0%), pediatric departments (3.6%), and dermatology departments (0.6%).

Thirty-five patients were excluded from the safety analysis due to missing safety data, and five patients were not eligible for inclusion as they did not complete the survey. The remaining 1355 patients were included in this analysis based on the availability of 5-year interim data. Two patients had missing efficacy data; therefore, the effectiveness analysis set consisted of 1353 patients. The renal prognosis analysis set consisted of 1142 patients (the effectiveness analysis set, excluding 211 patients who did not receive tacrolimus continuously for at least 28 weeks, had suffered from renal failure before start of tacrolimus treatment, or for whom renal failure was diagnosed within 28 weeks after starting tacrolimus treatment).

The patients were predominantly female (84.9%), with a mean ±SD age of 38.3 ±13.64 years. Durations of SLE and LN were 9.3 ±8.13 years and 6.7 ±7.03 years, respectively. Most patients had LN class IV or V (classified with the biopsy-proven pathologic type according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN (17)) (**Table 1**).

The tacrolimus continuation rate was 88.5% at week 28, 83.7% at 1 year and 62.7% at 5 years. Up to week 12, the main reason for tacrolimus discontinuation was AEs. After week 12, “unchanged/worsened symptoms” and “onset of AEs” accounted for

similar numbers of discontinuations (**Figure 1**). The mean ±SD follow-up period (including additional observational period after discontinuation of tacrolimus treatment) was 1817.4 ±996.26 days in this analysis.

Tacrolimus daily dose and blood concentration

The mean ±SD tacrolimus daily dose was 2.22 ±0.825 mg/day at baseline. The mean ±SD daily dose was similar at Year 1 (2.60 ±0.73 mg/day) and at Year 5 (2.58 ±0.74 mg/day). Mean tacrolimus blood concentrations were 4.3–4.7 ng/mL during Years 1–5 (**Supplementary Table 1**).

Safety

Among the safety analysis population of 1355 patients, 2098 ADRs were reported in 772 patients (57.0%). The most commonly observed ADRs included 83 cases (6.1%) of hypertension, 66 cases (4.9%) of nasopharyngitis, 59 cases (4.4%) of upper respiratory inflammation, 55 cases (4.1%) of diarrhea, 51 cases (3.8%) of herpes zoster and 45 cases (3.3%) of bronchitis. Common serious ADRs included 15 cases (1.1%) of pneumonia, 14 cases (1.0%) of herpes zoster, 13 cases (1.0%) of cellulitis, and 13 cases (1.0%) of diabetes mellitus.

Importantly, there was no marked increase in the incidence of any of the reported AEs, including serious ADRs, over the observed follow-up period (**Figure 2**). Of the ADRs of particular interest in the safety population, infections occurred in 353 patients (26.1%), followed by renal impairment in 137 patients (10.1%), neuropsychiatric disorders in 87 patients (6.4%), impaired glucose tolerance in 84 patients (6.2%), cardiac dysfunction in 27 patients (2.0%), malignant tumors (lymphomas) in 24 patients (1.8%), menstrual disorders in 13 patients (1.0%), and pancreatic dysfunction in 4 patients (0.3%). A worsening of interstitial pneumonia was not observed.

Subgroup analysis for the incidence of ADRs during the first 28 weeks of tacrolimus treatment suggested a higher risk of infection with concomitant or previous disease and in patients positive for urinary erythrocytes. A higher risk of renal disorders was seen with inpatient care, increasing age, abnormal renal or cardiac function, higher urinary protein and higher serum creatinine. A higher risk for glucose tolerance disorders was seen with inpatient care, increasing age, higher body mass index (BMI), abnormal liver function and higher tacrolimus blood concentrations (**Table 2**). No significant differences were observed in any of the subgroup analyses based on LN class.

Effectiveness

In the renal prognosis analysis set, the cumulative rates of progression to renal failure were 0.8% at Year 1, and 6.6% at Year 5; rates of progression to dialysis were 0% at Year 1, and 1.0% at Year 5. In the efficacy analysis set, the cumulative relapse rates were 7.8% at Year 1, and 30.6% at Year 5 (**Figure 3**).

Subgroup analysis of tacrolimus effectiveness over 5 years suggested that rates of progression to renal failure were higher in older patients and in those with higher BMI, concomitant or previous disease, abnormal renal or cardiac function, higher urinary protein and higher serum creatinine. Rates of dialysis were higher in patients with higher BMI, abnormal renal function and higher serum creatinine. Relapse rates were higher in inpatients, younger patients and patients positive for urinary erythrocytes. A statistically significant association was also seen between relapse rates and mean daily steroid dose (**Table 3**). No significant differences were observed in any of the subgroup analyses based on LN class.

UPCR was significantly decreased from 4 weeks after the initiation of tacrolimus treatment ($p<0.001$), and the effect was maintained at 5 years (**Supplementary**

Table 2). However, no clinically or statistically significant change was observed in creatinine clearance over the follow-up period (**Supplementary Table 2**). Serum anti-dsDNA antibody and complement C3 levels were significantly improved from 4 weeks ($p<0.001$), and the effect was also maintained to 5 years. The total daily dose of concomitant prednisolone fell significantly after the initiation of treatment with tacrolimus from 17.3 ±11.98 to 8.5 ±5.25 mg/day at 5 years ($p<0.001$) (**Supplementary Table 2**).

DISCUSSION

Maintenance therapy with prolonged immunosuppressive treatment is very important in LN, owing to the high relapse rate even after successful induction treatment. Ciruelo et al reported that successful induction treatment of LN with cyclophosphamide was associated with a relapse rate of approximately 25% after 5 years (18), and another report indicated that 37% of newly diagnosed LN patients experienced at least one renal flare, despite ongoing therapy with low-dose glucocorticoids and azathioprine in most patients (19). In the ALMS study, treatment failure rates in LN patients receiving maintenance therapy with mycophenolate mofetil and azathioprine after successful induction therapy were 16.4% and 32.4%, respectively, at 36 months (20).

There is increasing evidence to suggest that the immunosuppressant tacrolimus may be an effective and well-tolerated treatment option for LN as both induction and maintenance therapy (14,15,21–26); however, these data are largely based on short-term treatment and small patient populations. In particular, long-term data and data on its use as maintenance therapy are notably lacking. In 2014, Yap et al reported a retrospective study of 29 LN patients who received tacrolimus for 46.9 months, and concluded that the effectiveness of tacrolimus warranted further investigation as a long-term maintenance agent (27).

In this PMS study assessing the long-term safety and effectiveness of tacrolimus as LN maintenance therapy, the tacrolimus continuation rate at 5 years was 62.7%. The main reason for discontinuation of tacrolimus therapy in the early treatment period (up to week 28) was AEs, but this was a less frequent reason for discontinuation thereafter. This suggests that physicians should take care to judge whether discontinuation of tacrolimus due to AEs is warranted, taking into consideration the duration of therapy. The tacrolimus discontinuation rate of 37.3% in the present study can be compared to that observed with other immunosuppressive agents. In the 36-month, Phase 3 ALMS study comparing azathioprine and mycophenolate as

maintenance therapy for patients with LN, the discontinuation rate due to AEs was 39.6% for azathioprine and 25.2% with mycophenolate mofetil (20). However, lower discontinuation rates were reported at a mean follow-up of 48 months in the MAINTAIN Nephritis trial (17.3% for azathioprine and 28.3% with mycophenolate mofetil) (28).

The most common ADRs during the 5-year tacrolimus treatment period were infections, of which nasopharyngitis, herpes zoster and bronchitis were most frequent. The major ADRs, including infections, tended to develop early, without any marked increase over the duration of the follow-up period. This indicates that physicians should take care to adequately explain to their patients that major ADRs of tacrolimus are most likely to occur during the early treatment period and careful monitoring for ADRs is warranted, particularly during the initiation phase of tacrolimus treatment. There was no significant increase in the incidences of renal dysfunction and malignancy. No safety concerns with the long-term use of tacrolimus were seen in the current 5-year interim analysis.

Serum tacrolimus concentration is an important indicator for safe and effective LN management. Chen et al reported that with titration of tacrolimus to achieve a

relatively low trough blood concentration of 4–6 ng/mL, none of the tacrolimus-treated patients developed renal relapse during 6 months' maintenance therapy (15). Safety profiles were favorable with very low risks of nephrotoxicity, arterial hypertension, hyperlipidemia and other calcineurin inhibitor-related ADRs (15). The tacrolimus trough levels described by Chen et al are likely to guide tacrolimus administration dosage and trough level monitoring in clinical practice.

Subgroup analysis of the incidence of ADRs suggested that inpatient management, comorbidity or previous disease, severity of the underlying disease, increasing age and abnormal renal or liver function were risk factors for commonly observed ADRs of tacrolimus, such as infections, renal disorders and glucose tolerance disorders. Although almost all of these are already known risk factors (29,30), we believe that treatment with tacrolimus will be better tolerated if more careful attention is paid to the patients with these risk factors in real-world clinical practice.

Renal function parameters were improved in the first 4 weeks after the initiation of tacrolimus therapy, and sustained to 5 years. Improvements were observed for rates of progression to renal failure, dialysis and relapse, urine protein:creatinine ratio, anti-dsDNA antibody, serum complement C3, and concomitant prednisolone dose.

This further demonstrates stable renal function in patients with LN receiving long-term tacrolimus therapy in a real-world clinical practice setting, building on a previous small placebo-controlled, double-blind, multicenter study of tacrolimus therapy in LN of short duration (14).

This PMS study has a number of strengths. It is the first prospective observational study to assess the long-term safety and effectiveness of tacrolimus for LN maintenance therapy among a large patient population in a real-world clinical setting. The study population was enrolled from 275 sites across Japan, a feature that may make it more representative of LN patients in Asia, where substantial patient morbidity and mortality are reported (2,3,31). However, we think that the data obtained from this PMS study will also be useful outside of Asia and help to establish optimal tacrolimus treatment administration and monitoring worldwide.

Nevertheless, this study also has several limitations, including the incorrect completion of report forms, lack of protocol-defined definitions for effectiveness variables, and its open-label and non-comparative observational design, with the attendant potential for bias. Direct comparison with other standard maintenance therapies, such as azathioprine and mycophenolate mofetil, is missing here and

would be valuable in future studies. While this study aimed to include all patients with LN initiating maintenance treatment with tacrolimus in Japan, 14% of the target sites did not participate in the study. Without information on the number of patients receiving tacrolimus maintenance therapy for LN at these sites, it was challenging to estimate the overall patient coverage of the study. We believe that approximately 90% of patients with LN initiating maintenance treatment with tacrolimus in Japan were included. Although this is a lower proportion of patients than initially anticipated, it is considered sufficient to adequately reflect the real-world clinical setting in Japan. Finally, the results of this interim report should be regarded as preliminary in nature; as more data are collected, further analyses are planned.

In conclusion, this real-world study of tacrolimus as maintenance therapy in patients with LN showed that it is well tolerated and effective over 5 years. The final report of the ongoing PMS study at 10 years will shed further light on the clinical value and characterization of tacrolimus therapy in LN patients. Comparative studies against other immunosuppressive therapies are also required to determine the clinical utility and role of tacrolimus in this setting.

Acknowledgements: The authors wish to thank all investigators who participated in this study. Medical writing and editorial support was provided by Paola Accalai and Julia Donnelly for Cello Health MedErgy, funded by Astellas Pharma, Inc.

Data Statement:

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

References

1. Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. Nat Rev Nephrol. 2015;11:329–341.
2. Danchenko N, Satia J, Anthony M. Epidemiology of systematic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2006;12:308–318.
3. Osio-Salido E, Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. Lupus. 2010;19:1365–1373.
4. Korbet SM, Schwartz MM, Evans J, Lewis EJ. Severe Lupus Nephritis: Racial Differences in Presentation and Outcome. J Am Soc Nephrol. 2007;18:244–254.
5. Yap DYH, Lai KN. Pathogenesis of renal disease in Systemic Lupus Erythematosus—the role of autoantibodies and lymphocytes subset abnormalities. Int J Mol Sci. 2015;16:7917–7931.
6. Rahman A, Isenberg DA. Systemic Lupus Erythematosus. N Engl J Med. 2008;358:929–939.
7. Lech M, Anders H-J. The Pathogenesis of Lupus Nephritis. J Am Soc Nephrol. 2013;24:1357–1366.
8. Schwartz N, Goilav B, Putterman C. The pathogenesis, diagnosis and treatment of lupus nephritis. Curr Opin Rheumatol. 2014;26:502–509.

9. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110–2121.

10. Balow JE, Austin HA. Maintenance therapy for lupus nephritis — something old, something new. N Engl J Med. 2004;350:1044–1046.

11. Rovin BH, Parikh S V. Lupus nephritis: the evolving role of novel therapeutics. Am J Kidney Dis. 2014;63:677–690.

12. Kuiper-Geertsma DG, Derksen RH. Newer drugs for the treatment of lupus nephritis. Drugs. 2003;63:167–180.

13. Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus – a further update of its use in the management of organ transplantation. Drugs. 2003;63:1247–1297.

14. Miyasaka N, Kawai S, Hashimoto H. Efficacy and safety of tacrolimus for lupus nephritis: A placebo-controlled double-blind multicenter study. Mod Rheumatol. 2009;19:606–615.

15. Chen W, Liu Q, Chen W, Tang X, Fu P, Liu F, et al. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. Lupus. 2012;21:944–952.

16. Package insert of Prograf® Capsules 0.5 mg and 1 mg (tacrolimus hydrate). Astellas Pharma Inc.

17. Weening JJ, D'Agati VD, Schwartz MM, Seshan S V, Alpers CE, Appel GB, et

al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004;65:521–530.

18. Ciruelo E, De La Cruz J, López I, Gómez-Reino JJ. Cumulative rate of relapse of lupus nephritis after successful treatment with cyclophosphamide. Arthritis Rheum. 1996;39:2028–2034.

19. El Hachmi M, Jadoul M, Lefèbvre C, Depresseux G, Houssiau FA. Relapses of lupus nephritis: Incidence, risk factors, serology and impact on outcome. Lupus. 2003;12:692–696.

20. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886–1895.

21. Tanaka H, Oki E, Tsuruga K, Yashiro T, Hanada I, Ito E. Management of young patients with lupus nephritis using tacrolimus administered as a single daily dose. 2009;72:430–437.

22. Chen W, Tang X, Liu Q, Chen W, Fu P, Liu F, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis. 2011;57:235–244.

23. Li X, Ren H, Zhang Q, Zhang W, Wu X, Xu Y, et al. Mycophenolate mofetil or

tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant. 2012;27:1467–1472.

24. Mok CC, Tong KH, To CH, Siu YP, Au TC. Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study. Kidney Int. 2005;68:813–817.

25. Bao H, Liu Z-H, Xie H-L, Hu W-X, Zhang H-T, Li L-S. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol. 2008;19:2001–2010.

26. Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016;75:30–36.

27. Yap DYH, Ma MKM, Mok MMY, Kwan LPY, Chan GCW, Chan TM. Long-term data on tacrolimus treatment in lupus nephritis. Rheumatology. 2014;53:2232–2237.

28. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69:2083–2089.

29. Takahashi K, Abe R, Usuki S, So M. Safety and efficacy of once-daily modified-release tacrolimus in kidney transplant recipients: Interim analysis of multicenter postmarketing surveillance in Japan. Transplant Proc. 2014;46:406–410.

30. Takeuchi T, Kawai S, Yamamoto K, Harigai M, Ishida K, Miyasaka N. Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3,267 Japanese patients with rheumatoid arthritis. Mod Rheumatol. 2014;24:8–16.

31. Yap DYH, Chan TM. Lupus Nephritis in Asia: Clinical Features and Management. Kidney Dis. 2015;1:100–109.

Figure legends

Figure 1. Treatment continuation rate with tacrolimus (efficacy analysis set)

TAC, tacrolimus

Figure 2. Cumulative incidence of (A) adverse drug reactions, and (B) serious adverse drug reactions (safety analysis set)

Figure 3. Cumulative rates of progression to renal failure, progression to dialysis, and relapse (renal prognosis analysis set)

Supplementary Figure 1. Patient disposition

*A total of 18 patients with more than one reason for exclusion from the renal prognosis analysis set were only counted once in the overall total of excluded patients.

CRF, case report form

Tables

Table 1: Baseline demographics and clinical characteristics (safety analysis set)

Parameter	Patients (N =1355)
Sex	
Male	205 (15.1)
Female	1150 (84.9)
Age, years, mean ±SD	38.3 ±13.64
Duration of SLE, years, mean ±SD	9.3 ±8.13
Duration of LN, years, mean ±SD	6.7 ±7.03
Anti-phospholipid syndrome	192 (14.2)
Previous treatment	
Mizoribine	311 (23.0)
Cyclosporine	171 (12.6)
Azathioprine	73 (5.4)
Cyclophosphamide	72 (5.3)
Mycophenolate mofetil	30 (2.2)
Pathologic type (ISN/RPS 2003 classification)	
Type I	9 (0.7)
Type II	68 (5.0)

Type II+V	7 (0.5)
Type III	73 (5.4)
Type III+V	26 (1.9)
Type IV-S	64 (4.7)
Type IV-S+V	15 (1.1)
Type IV-G	149 (11.0)
Type IV-G+V	23 (1.7)
Type V	156 (11.5)
Type VI	1 (0.1)
Other	28 (2.1)

SD: standard deviation, SLE: systemic lupus erythematosus, LN: lupus nephritis,

ISN/RPS: International Society of Nephrology/Renal Pathology Society

Data are n (%) unless indicated otherwise

Table 2: Subgroup analysis of the incidence of ADRs occurring during 28 weeks of treatment with tacrolimus (safety analysis set)

Patient characteristics at baseline		**N**	**Infections, n (%)**	**p value**	**Renal disorders, n (%)**	**p value**	**Glucose tolerance disorders, n (%)**	**p value**
Therapy setting	Inpatients	306	39 (12.8)	0.134*	20 (6.5)	0.039*	19 (6.2)	0.004*
	Outpatients	1049	101 (9.6)		39 (3.7)		27 (2.6)	
Age (years)	<15	25	3 (12.0)	0.054#	0	0.006#	0	0.015#
	15–29	352	32 (9.1)		10 (2.8)		6 (1.7)	
	30–39	399	36 (9.0)		17 (4.3)		13 (3.3)	
	40–49	296	35 (11.8)		12 (4.1)		14 (4.7)	
	50–64	229	20 (8.7)		15 (6.6)		10 (4.4)	
	≥65	54	14 (25.9)		5 (9.3)		3 (5.6)	

BMI (kg/m²)	<25 25–30 >30	798 148 42	86 (10.8) 18 (12.2) 5 (11.9)	0.635#	37 (4.6) 7 (4.7) 2 (4.8)	0.954#	24 (3.0) 9 (6.1) 3 (7.1)	0.031#
Concomitant disease	Absence Presence	166 1192	7 (4.3) 133 (11.2)	0.006*	4 (2.5) 55 (4.6)	0.302*	2 (1.2) 44 (3.7)	0.160*
Previous disease	Absence Presence	931 366	80 (8.6) 50 (13.7)	0.008*	33 (3.5) 22 (6.0)	0.065*	28 (3.0) 16 (4.4)	0.234*
Liver function	Normal Abnormal	1256 96	128 (10.2) 12 (12.5)	0.486*	54 (4.3) 5 (5.2)	0.605*	35 (2.8) 11 (11.5)	<0.001*
Renal function	Normal Abnormal	1061 293	104 (9.8) 36 (12.3)	0.233*	29 (2.7) 30 (10.2)	<0.001*	35 (3.3) 11 (3.8)	0.716*
Cardiac function	Normal	1271	128 (10.1)	0.118*	52 (4.1)	0.037*	40 (3.1)	0.121*

	Abnormal	58	10 (17.2)		6 (10.3)		4 (6.9)	
Urinary protein	−	322	31 (9.6)	0.156#	5 (1.6)	0.003#	8 (2.5)	0.616#
(qualitative)	±	128	11 (8.6)		4 (3.1)		4 (3.1)	
	+	217	16 (7.4)		11 (5.1)		12 (5.5)	
	++	279	31 (11.1)		14 (5.0)		10 (3.6)	
	3+, 4+	291	37 (12.7)		18 (6.2)		9 (3.1)	
Urinary erythrocyte	−	547	35 (6.4)	<0.001#	18 (3.3)	0.264#	17 (3.1)	0.992#
count	±	151	19 (12.6)		11 (7.3)		7 (4.6)	
(qualitative)	+	198	27 (13.6)		8 (4.0)		8 (4.0)	
	++	152	25 (16.4)		6 (3.9)		6 (3.9)	
	3+, 4+	129	15 (11.6)		8 (6.2)		3 (2.3)	

Serum creatinine	<0.8	944	100 (10.6)	0.976#	27 (2.9)	<0.001#	30 (3.2)	0.523#
(mg/dL)	0.8–1.1	232	21 (9.1)		14 (6.0)		9 (3.9)	
	1.2–1.5	90	9 (10.0)		9 (10.0)		5 (5.6)	
	≥1.6	45	6 (13.3)		9 (20.0)		1 (2.2)	
TAC daily dose	<3	788	81 (10.3)	0.986#	40 (5.1)	0.150#	23 (2.9)	0.095#
(mg/day)	3.0	541	57 (10.5)		18 (3.3)		20 (3.7)	
	>3	25	2 (8.0)		1 (4.0)		3 (12.0)	
TAC blood trough	<5	692	51 (7.4)	0.243#	26 (3.7)	0.169#	17 (2.4)	0.038#
concentration (ng/mL)	5–<10	271	21 (7.8)		11 (4.0)		14 (5.1)	
	10–<15	20	4 (20.0)		3 (15.0)		1 (4.8)	

The subgroup analyses were performed for the incidences of common adverse drug reactions (ADRs) occurring during the first 28-weeks of treatment with tacrolimus (TAC). The incidence of infections, renal disorders and glucose tolerance disorders were analyzed as common ADRs.

*Fisher's exact test, #Cochran–Armitage trend test

–, negative; ±, pseudo-positive; +, positive; ++ double positive; 3+/4+, strong positive

Table 3: Subgroup analysis of the incidence of renal failure, rate of progression to dialysis and relapse at Year 5 (renal prognosis analysis set)

Patient characteristics at baseline		**N**	**Renal failure; Cumulative incidence (95% CI)**	**p value***	**Dialysis; Cumulative incidence (95% CI)**	**p value***	**N**	**Relapse; Cumulative incidence (95% CI)**	**p value***
Sex	Male	172	9.1 (5.5–14.9)	0.077	0.7(0.1–4.6)	0.775	204	37.2 (29.8–45.8)	0.176
	Female	970	6.2 (4.7– 8.1)	0.121	1.0 (0.5–2.1)	0.729	1149	29.4 (26.4–32.7)	0.102
Therapy setting	Inpatients	236	4.7 (2.5–8.8)	0.215	1.1 (0.3–4.2)	0.828	306	38.6 (31.9–46.0)	0.017
	Outpatients	906	7.1 (5.5–9.2)	0.214	1.0 (0.5–2.0)	0.863	1047	28.6 (25.6–32.0)	0.029
Age (years)	<15	23	0 (0–0)	0.039	0 (0–0)	0.954	25	42.7 (24.7–66.4)	<0.001
	15–29	312	3.7 (2.0–6.8)	0.030	1.2 (0.4–3.6)	0.956	352	44.4 (38.6–50.8)	<0.001

	30–39	341	6.6 (4.2–10.2)		0.8 (0.2–3.0)		398	28.0 (23.0–33.8)	
	40–49	259	6.8 (4.2–11.1)		1.0 (0.2–3.8)		296	26.3 (21.0–32.6)	
	50–64	172	11.4 (7.1–18.0)		1.5 (0.4–5.8)		228	18.1 (12.9–25.2)	
	≥65	35	14.4 (5.6–34.1)		0 (0–0)		54	21.0 (9.9–41.3)	
BMI (kg/m^2)	<25	671	5.3 (3.7–7.5)	0.039	0.4 (0.1–1.5)	<0.001	797	32.4 (28.6–36.4)	0.771
	25–30	119	10.9 (6.0–19.3)	0.030	1.1 (0.2–7.8)	<0.001	148	29.9 (22.1–39.6)	0.833
	>30	30	14.6 (5.7–34.3)		7.1 (1.8–25.7)		42	36.0 (21.3–56.4)	
Concomitant	Absence	144	0 (0–0)	0.002	0 (0–0)	0.253	162	32.1 (24.3–41.6)	0.847
disease	Presence	997	7.6 (6.0–9.6)	0.002	1.1 (0.6–2.2)	0.253	1190	30.3 (27.3–33.5)	0.773
Previous	Absence	797	4.2 (2.9–6.0)	<0.001	0.7 (0.2–1.7)	0.156	930	30.3 (26.9–34.0)	0.252
disease	Presence	299	11.9 (8.5–16.5)	<0.001	1.6 (0.6–4.1)	0.178	366	33.9 (28.5–40.1)	0.266

Liver function	Normal	1065	6.9 (5.4–8.7)	0.268	0.9 (0.5–1.9)	0.529	1254	30.7 (27.8–33.9)	0.818
	Abnormal	74	3.7 (0.9–14.0)	0.300	1.9 (0.3–12.4)	0.517	96	30.1 (20.1–43.5)	0.869
Renal function	Normal	954	3.9 (2.7–5.5)	<0.001	0.5 (0.2–1.4)	<0.001	1060	29.7 (26.6–33.1)	0.158
	Abnormal	187	20.8 (15.2–28.0)	<0.001	3.4 (1.4–8.0)	<0.001	292	34.2 (27.9–41.4)	0.166
Cardiac function	Normal	1081	6.2 (4.8–8.0)	0.009	1.0 (0.5–2.0)	0.620	1269	31.2 (28.2–34.3)	0.766
	Abnormal	39	17.9 (7.8–38.1)	0.010	0 (0–0)	0.620	58	24.1 (12.9–42.3)	0.603
Urinary protein, qualitative	−	286	1.8 (0.7–4.7)	<0.001	0 (0.0)	0.166	322	27.6 (22.3–33.9)	0.071
	±	116	3.1 (1.0–9.5)	<0.001	0 (0–0)	0.175	128	29.4 (21.2–39.9)	0.073
	+	188	7.5 (4.3–12.8)		1.3 (0.3–5.1)		217	26.8 (20.6–34.4)	
	++	229	9.5 (6.1–14.7)		1.7 (0.6–5.2)		278	32.6 (26.5–39.8)	
	3+, 4+	229	11.6 (7.8–17.0)		2.1 (0.8–5.6)		290	38.8 (32.2–46.1)	

Urinary	−	481	6.2 (4.2–9.0)	0.269	0.8 (0.3–2.5)	0.366	546	26.4 (22.3–31.1)	0.002
erythrocyte	±	115	7.3 (3.5–14.8)	0.222	2.2 (0.6 – 8.7)	0.413	151	36.6 (28.1–46.7)	0.007
count,	+	168	11.1 (7.0–17.5)		2.1 (0.7–6.3)		197	37.0 (29.7–45.4)	
qualitative	++	126	4.0 (1.5–10.3)		0 (0–0)		152	36.4 (28.0–46.5)	
	3+, 4+	103	5.4 (2.3–12.7)		1.3 (0.2–8.6)		129	38.0 (28.4–49.5)	
Serum	<0.8	849	3.2 (2.1–4.9)	<0.001	0.5 (0.1–1.4)	<0.001	943	30.0 (26.7–33.6)	0.893
creatinine	0.8–1.1	192	11.2 (7.3–17.0)	<0.001	0.6 (0.1–4.3)	<0.001	232	35.1 (28.3–43.0)	0.790
(mg/dL)	1.2–1.5	55	34.1 (22.7–		6.2 (2.0–18.1)		89	32.0 (21.5–46.1)	
	≥1.6	10	49.1)		14.3 (2.1–66.6)		45	22.5 (11.3–41.7)	
			33.3 (12.2–						
			71.8)						
Steroid dose	<10	555	5.1 (3.5–7.5)	0.097	0.6 (0.2–2.0)	0.714	602	19.9 (16.6–23.8)	<0.001

(mg/day)	10–19	515	7.8 (5.6–10.8)	0.099	1.2 (0.5–2.9)	0.708	609	40.7 (36.1–45.7)	<0.001
	20–29	54	15.0 (7.0–30.5)		3.0 (0.4–19.6)		90	51.8 (37.7–67.6)	
	30–39	5	0 (0–0)		0 (0–0)		19	31.3 (7.4–83.7)	
	≥40	3	0 (0–0)		0 (0–0)		18	20.0 (3.1–79.6)	
TAC dose	<3	765	6.5 (4.8–8.7)	0.342	0.9 (0.4–2.1)	0.759	915	29.1 (25.7–32.7)	0.005
(mg/day)	3.0	324	7.8 (5.1–11.9)	0.353	1.3 (0.4–4.0)	0.733	380	32.5 (27.0–38.7)	0.021
	>3	52	2.3 (0.3–15.1)		0 (0–0)		57	43.3 (30.9–58.1)	

The subgroup analyses were performed for the incidences of renal failure, rate of progression to dialysis and relapse occurring during 5-year treatment of tacrolimus (TAC) to investigate the patient characteristics affecting the effectiveness outcomes. The Kaplan–Meier method was used to estimate cumulative incidence.

*Upper value, generalized Wilcoxon test; lower value, log-rank test

–, negative; ±, pseudo-positive; +, positive; ++ double positive; 3+/4+, strong positive

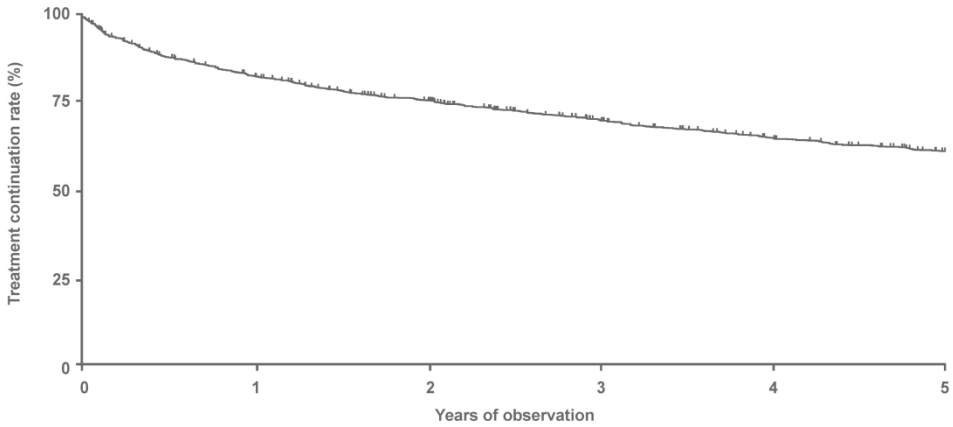

Figure 1. Treatment continuation rate with tacrolimus (efficacy analysis set)TAC, tacrolimus

174x100mm (600 x 600 DPI)

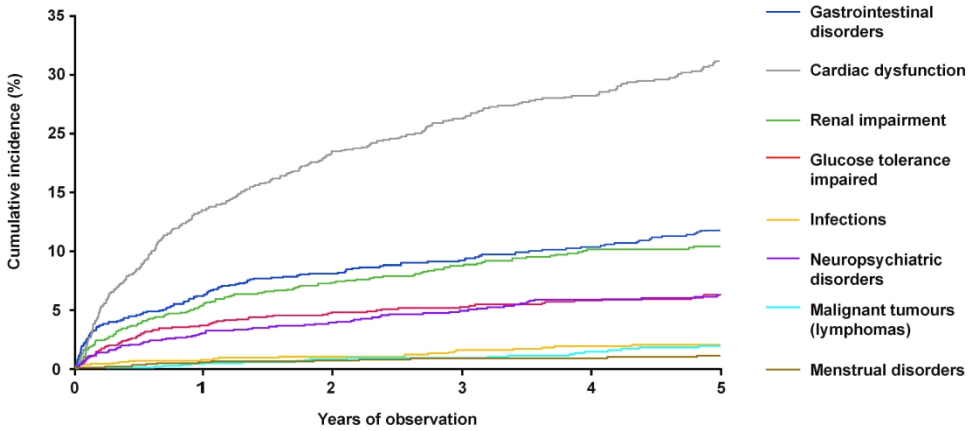

Figure 2. Cumulative incidence of (A) adverse drug reactions, and (B) serious adverse drug reactions (safety analysis set)

174x100mm (600 x 600 DPI)

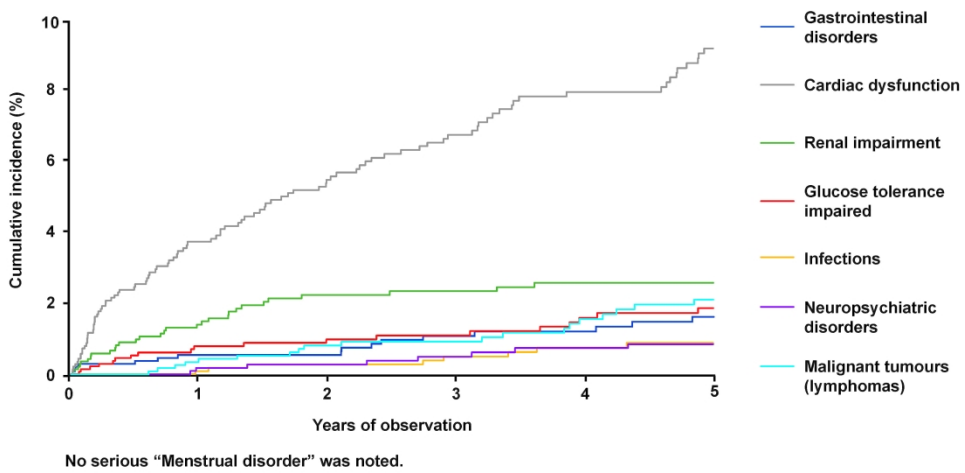

Figure 2. Cumulative incidence of (A) adverse drug reactions, and (B) serious adverse drug reactions (safety analysis set)

174x100mm (600 x 600 DPI)

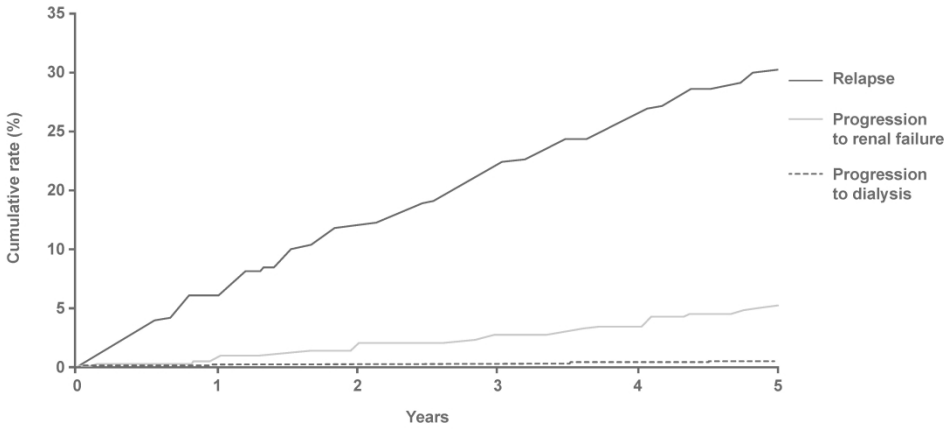

Figure 3. Cumulative rates of progression to renal failure, progression to dialysis, and relapse (renal prognosis analysis set)

174x100mm (600 x 600 DPI)