

## Treatment of young patients with lupus nephritis using calcineurin inhibitors

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transcription of the early activation genes of interleukin (IL)-2 and suppressing T cell-induced activation of tumor necrosis factor- $\alpha$ , IL-1 $\beta$  and IL-6. Therefore, both drugs, which we believe may be less cytotoxic, are attractive therapeutic options for young patients with lupus nephritis. Recently, a multidrug regimen of prednisolone (PDN), Tac, and mycophenolate mofetile (MMF) has been found effective and relatively safe in adult lupus nephritis. Since the mechanisms of action of MMF and Tac are probably complementary, multidrug therapy for lupus nephritis may be useful. We propose as an alternative to IVCY, a multidrug therapy with mizoribine, which acts very similarly to MMF, and Tac, which has a different mode of action, combined with PDN for pediatric-onset lupus nephritis. We also believe that a multidrug therapy including CsA and Tac may be an attractive option for young patients with SLE and lupus nephritis

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### Abstract

Recent advances in the management of lupus nephritis, together with earlier renal biopsy and selective use of aggressive immunosuppressive therapy, have contributed to a favorable outcome in children and adolescents with systemic lupus erythematosus (SLE). Nevertheless, we believe that a more effective and less toxic treatment is needed to attain an optimal control of the activity of lupus nephritis. Recent published papers and our experiences regarding treatment of young patients with lupus nephritis using calcineurin inhibitors are reviewed. Although it has been reported that intermittent monthly pulses of intravenous cyclophosphamide (IVCY) are effective for preserving renal function in adult patients, CPA is a potent immunosuppressive agent that induces severe toxicity, including myelo- and gonadal toxicity, and increases the risk of secondary malignancy. Thus, treatment for controlling lupus nephritis activity, especially in children and adolescents, remains challenging. Cyclosporine A (CsA) and tacrolimus (Tac) are T-cell-specific calcineurin inhibitors that prevent the activation of helper T cells, thereby inhibiting the

### INTRODUCTION

Recent advances in the management of lupus nephritis, together with earlier renal biopsy and selective use of ag-

gressive immunosuppressive therapy, have contributed to a favorable outcome in children and adolescents with systemic lupus erythematosus (SLE)<sup>[1]</sup>. Since SLE is a chronic disease associated with frequent disease flares, effective and safe maintenance therapy is needed to reduce the risk of such flares<sup>[2-4]</sup>. Thus, treatment for lupus nephritis in adolescents remains challenging. Intermittent monthly pulses of intravenous cyclophosphamide (IVCY) have been reported to be effective even for patients with pediatric-onset SLE<sup>[5]</sup>; however, CY is a potent immunosuppressive agent associated with myelotoxicity, gonadal toxicity, and an increased risk of secondary malignancy<sup>[3,6]</sup>. Since therapy-related adverse events are a major therapeutic risk of immunosuppressive treatment in patients with SLE, selecting a safe and effective treatment protocol poses a major dilemma for physicians treating young patients. Cyclosporine A (CsA) and tacrolimus (Tac) are expected to be effective in patients with SLE and lupus nephritis, because of their strong suppressive effects on activated T cells. Indeed, CsA and Tac have been found useful to treat difficult cases of adult lupus nephritis<sup>[7-18]</sup>. These studies found that both CsA and Tac ameliorated the clinical activity of SLE and exerted an anti-proteinuric effect in lupus nephritis. Therefore, we hypothesized that calcineurin inhibitors might be a feasible alternative for maintenance treatment, and sometimes for induction treatment, in young patients with lupus nephritis<sup>[19-21]</sup>. Recently, a multidrug regimen comprising prednisolone (PDN), Tac, and mycophenolate mofetile (MMF) was found safe and effective in adult lupus nephritis<sup>[22-24]</sup>. In this mini review, we would like to discuss the efficacy and safety of treatment using a relatively low-dose of CsA and Tac in young patients with lupus nephritis. Furthermore, we would like to discuss the potential usefulness of a multidrug therapy consisting of mizoribine (MZR), a selective inhibitor of inosine monophosphate dehydrogenase in the *de novo* pathway of purine nucleotides that acts very similar to MMF, and Tac, which has a different mode of action, combined with PDN, in the treatment of pediatric-onset SLE<sup>[25]</sup>.

## CYCLOSPORINE A TREATMENT

CsA has been reported to selectively inhibit the nuclear factor of activated T cell signaling, and thereby reduce (interleukin) IL-2 synthesis and suppress lymphocyte proliferation<sup>[9]</sup>. These immunosuppressive effects result in the decrease of autoantibody-mediated production and glomerular deposition of immune complexes. Furthermore, it has been shown recently that CsA stabilizes the podocyte actin cytoskeleton leading to maintenance of the integrity of the glomerular filtration barrier<sup>[26]</sup>. This mechanism reasonably explains the strong anti-proteinuric effect of CsA. Thus, CsA is expected to suppress lupus nephritis activity, decrease urinary protein excretion and preserve renal function<sup>[7-11]</sup>. Recently, Zavada *et al*<sup>[10]</sup> performed a prospective randomized trial of CsA compared to IVCY in 40 adults patients with proliferative

lupus nephritis, and concluded that treatment with CsA (the initial dose of the drug, 4-5 mg/kg per day) was as effective as IVCY concerning sequential induction, maintenance treatment, and preservation of renal function<sup>[10]</sup>. In their study, adverse events were infrequent, but transient increases in serum creatinine, hypertension and generalized seizures were noted in some patients. Thus, although CsA-related clinical toxicities, such as hypertension, hypertrichosis, gingival hyperplasia, posterior reversible encephalopathy syndrome and nephrotoxicity remain therapeutic risks, these were less severe than those observed with IVCY<sup>[7-9]</sup>. More recently, treatment with a relatively low dose of CsA of approximately 2.5 mg/kg per day and a blood trough level of around 100 ng/mL was found effective and safe for patients with SLE and lupus nephritis<sup>[11,27]</sup>. Interestingly, it has lately been reported that both CsA and Tac may overcome treatment unresponsiveness through a blockade of the drug exclusion effect of P-glycoprotein (P-gp), leading to restoration of the intracellular therapeutic levels of corticosteroids and clinical improvement<sup>[28,29]</sup>. In order to inhibit P-gp, even low-dose CsA could competitively inhibit the excretion of intracellular corticosteroids through P-gp on lymphocytes, thus overcoming corticosteroid resistance and leading to improvement of the clinical features of SLE<sup>[29]</sup>. These laboratory observations have suggested that CsA, even at a low dose, might have other useful mechanisms of action besides its immunosuppressive effects. This would warrant its use in patients with active and steroid-resistant SLE with lupus nephritis.

Concerning CsA treatment for young patients with lupus nephritis, several reports of single cases or case series have been published to date<sup>[19,30-33]</sup>. Baca *et al*<sup>[31]</sup> reported that low-dose CsA (2-4 mg/kg per day with a median blood trough level of the drug 57 ng/mL) was effective and safe in 7 children with proliferative lupus nephritis resistant to cytotoxic therapy; however, relapses were common after discontinuation of treatment with CsA for one year. Aragon *et al*<sup>[32]</sup> reported on the efficacy of CsA (3-6 mg/kg per day with a blood trough level of the drug 100-200 ng/mL) in their retrospective cohort of 13 children with severe lupus nephritis following intravenous high-dose methylprednisolone pulse therapy (MPT) combined with MMF. They found a significant anti-proteinuric effect of CsA as well as suppression of the disease activity. Regarding histologic changes, Kawasaki *et al*<sup>[33]</sup> reported that treatment with low-dose CsA for 24 mo (2-2.5 mg/kg per day with a blood trough level of the drug 60-75 ng/mL) was effective and safe in a 17-year-old Japanese patient with diffuse proliferative lupus nephritis [World Health Organization (WHO) class IVc lupus nephritis]. Repeat renal biopsy confirmed histological improvement (WHO class II lupus nephritis) without CsA-related renal toxicities<sup>[33]</sup>. We reported successful treatment with very low-dose CsA in a 6-year-old Japanese girl with WHO class III lupus nephritis resistant to IVCY<sup>[19]</sup>. In our patient, CsA at a dose of 1.8 mg/kg per day was administered once daily and resulted in a sufficient 0-4 h area under

the time concentration curve ( $AUC_{0-4}$ , approximately 2000 ng  $\times$  h/mL), comparable with the results in stable renal transplant patients receiving the drug in the maintenance phase<sup>[34]</sup>, without any adverse events. These clinical observations suggested the potential usefulness of CsA administered at a relatively low dose to young patients with lupus nephritis. Since therapy-related clinical toxicities remain a major concern, we think that an optimal CsA treatment strategy for lupus nephritis, using the lowest possible dose of CsA to minimize treatment toxicity, while maintaining its efficacy, has been long desired. In this context, we suggest that once-daily administration of CsA prevented progression of chronic CsA nephrotoxicity, and that the administration of low doses of CsA following a once-daily protocol shortened the exposure to the drug<sup>[11,19]</sup>. Concerning  $AUC_{0-4}$  values of CsA, it has been reported that around 2000 ng  $\times$  h/mL might be appropriate for renal transplant patients in the maintenance phase<sup>[34]</sup>, although the most appropriate target  $AUC_{0-4}$  value of CsA to treat lupus nephritis remains speculative. These clinical observations show that CsA could be an attractive alternative to classic cytotoxic agents<sup>[35]</sup>. However, there is no data regarding long-term results of treatment with CsA in young patients with lupus nephritis. Thus, further studies involving a larger number of young patients with lupus nephritis would be needed to confirm the efficacy and safety of CsA in the treatment of pediatric-onset lupus nephritis.

## TACROLIMUS TREATMENT

Like CsA, Tac is a T cell-specific calcineurin inhibitor that prevents activation of helper T cells, thereby inhibiting the transcription of the early activation genes of IL-2 and suppressing the production of tumor necrosis factor (TNF)- $\alpha$ , IL-1 $\beta$ , and IL-6. Considering its effects, Tac is also expected to be effective in patients with active SLE and lupus nephritis<sup>[12-18]</sup>. To date several papers have described the efficacy and safety of Tac combined with PDN, administered without showing serious adverse effects, as induction and maintenance therapy to patients with proliferative and membranous lupus nephritis<sup>[12-18,20,21]</sup>. The safety of Tac treatment is important because of its potent nephrotoxicity. Although these patients did not necessarily have permanently high blood levels of Tac<sup>[14]</sup>, the development of an optimal Tac treatment strategy for lupus nephritis, with a dose as low as possible, is sought to minimize treatment toxicity while maintaining treatment efficacy. In this context, in Japan, Tac is usually administered once daily to patients with rheumatoid arthritis (RA) or lupus nephritis since once-daily administration of Tac is the governmental approved protocol<sup>[16,20,21,36,37]</sup>. It has been reported that Tac administered at a dose of 1.5-3.0 mg once daily for the treatment of RA is safe even in the elderly<sup>[36]</sup>. Although further studies, including a histologic evaluation following Tac treatment, are needed, we consider that a once-daily regimen could shorten the exposure to Tac, would be more

cost-beneficial than the conventional twice-daily protocol, and might result in better treatment compliance. Interestingly, Tac has been reported to stimulate glucocorticoid receptor (GR) transactivity through its ligands<sup>[38]</sup>, which may explain the tendency to exacerbate glucose intolerance in selected patients. However, some patients who had experienced new flares of SLE while receiving CsA were successfully treated with Tac<sup>[20,21]</sup>. Differential control of the GR hormone-binding function by immunosuppressive ligands, such as Tac, reportedly stimulates GR transactivity beyond the effect of the ligand on hormone retention although this is not the case with CsA<sup>[38]</sup>. These laboratory observations may explain the superior effect of Tac to that of CsA in selected patients with lupus, although this hypothesis remains speculative. Furthermore, it has been reported that Tac reduces proteinuria and mesangial alterations due to its suppressive effects on glomerular expression of IFN- $\gamma$  mRNA in rat models<sup>[39]</sup>. In addition, it has lately been reported that Tac, as well as CsA, may overcome treatment unresponsiveness through the blockade of the drug exclusion effect of P-gp, leading to restoration of the intracellular therapeutic levels of corticosteroids and clinical improvement<sup>[28,29]</sup>. These observations suggest that Tac might have other useful mechanisms of action besides its immunosuppressive effects, which would warrant its use in patients with active and steroid-resistant SLE with lupus nephritis.

In this regard, we have used Tac monotherapy at a relatively low dose for disease flare that was effective and safe<sup>[40]</sup>. A 38-year-old woman with a 24-year history of SLE and lupus nephritis suddenly presented significant proteinuria, arthralgia, hypocomplementemia and elevation of serum anti-dsDNA antibody titers. She had already shown active SLE with nephrotic-range proteinuria when she was 14 years old. Percutaneous renal biopsy revealed WHO class IVb diffuse proliferative lupus nephritis. After induction therapy consisting of MPT and oral CY, the disease activity, both clinical and serological, had been under reasonably good control during maintenance therapy. After a 2-year treatment, PDN was successfully discontinued, and she had remained free of SLE/lupus nephritis signs for over 20 years without medication. Although she had normal blood pressure and normal renal function at the flare, significant proteinuria associated with hypocomplementemia and elevation of serum anti-dsDNA antibody titers occurred. Nevertheless, the patient strongly refused to take PDN, mainly because of the risk of cosmetic adverse effects. Thus, we decided to treat her with Tac monotherapy. After obtaining written informed consent, Tac was administered at a dose of 3 mg/d (0.06 mg/kg) once daily after the evening meal. One month after the start of the protocol, a significant decrease in the European Consensus Lupus Activity Measurement (ECLAM) index was noted. After 3 mo of treatment, the improvement in the ECLAM index was associated with a significant decrease in the urinary protein excretion and marked recovery of hypocomplementemia. After 6 mo of treatment, the serum anti-dsDNA antibody titer showed a marked

**Table 1 Published reports of calcineurin inhibitor therapy in pediatric-onset lupus nephritis**

Authors (Ref.)	Drugs	Cases	Nephritis class	Dose of the drug	Follow-up period	Efficacy	Adverse effects
Sakano <i>et al</i> <sup>[30]</sup>	CsA	1	WHO class V	1.6 mg/kg with the 4 h area under the time concentration curve of the drug 554.5 ng × h/mL	12 mo	SLEDAI depression, Serological improvement and concomitantly administered PDN reduction	None
Baca <i>et al</i> <sup>[31]</sup>	CsA	7	WHO class IV and V	1.5-3 mg/kg with a mean trough blood level of the drug 57.1 ng/mL	12 mo	SLEDAI depression and urinary protein excretion decrease	Hypertension, hypertrichosis and mild gingival hyperplasia
Suzuki <i>et al</i> <sup>[19]</sup>	CsA	1	WHO class III	1.8 mg/kg with area under the time concentration curve of the drug approximately 2000 ng × h/mL	3 mo	Serological improvement and concomitantly administered PDN reduction	None
Kawasaki <i>et al</i> <sup>[33]</sup>	CsA	1	WHO class IV	2-2.5 mg/kg with trough blood level of the drug 60-75 ng/mL	24 mo	Histological improvement (WHO class II) and extrarenal signs improvement	Hirsutism
Aragon <i>et al</i> <sup>[32]</sup>	CsA	13	WHO class III and IV	3-6 mg/kg with trough blood level of the drug, 100-200 ng/mL	12 mo	SLEDAI depression, Serological improvement and urinary protein excretion decreases	Minor infections and herpes zoster
Tanaka <i>et al</i> <sup>[20]</sup>	Tac	6	WHO class II, IV and V	3 mg/d with trough blood level of approximately 5 ng/mL	6 mo	ECLAM depression, Serological improvement and concomitantly administered PDN reduction	None
Tanaka <i>et al</i> <sup>[21]</sup>	Tac	11	WHO class II, IV and V	3 mg/d with trough blood level of approximately 5 ng/mL	Up to 24 mo	ECLAM depression, Serological improvement and concomitantly administered PDN reduction	Minor infections and herpes zoster

CsA: Cyclosporine A; Tac: Tacrolimus; WHO: World Health Organization; PDN: Prednisolone; SLEDAI: Systemic lupus erythematosus disease activity index; ECLAM: European consensus of lupus activity measurement index.

tendency towards a decrease, with the serum creatinine level remaining unchanged. The blood levels of Tac were maintained relatively low at < 5.0 ng/mL. No adverse reaction to Tac treatment was observed. At present, after 14 mo of treatment, she is free from SLE/lupus nephritis signs except for a slight increase in the serum anti-dsDNA antibody titers during treatment with Tac monotherapy at a dose of 3 mg/d. This clinical observation suggested that Tac, even as a sole agent, may be potentially effective in selected patients with lupus nephritis<sup>[40]</sup>.

Although the efficacy and safety of Tac in young patients with lupus nephritis has rarely been reported so far, we treated 11 consecutive patients with long-standing biopsy-proven lupus nephritis with low-dose Tac (3 mg/d, 0.04-0.075 mg/kg) under a once-daily administration protocol for a mean of 18 mo (6-24 mo)<sup>[21]</sup>. As a result, despite the gradual tapering of the PDN dose, a marked improvement in the ECLAM index, compared with baseline values, was observed even at 1 mo after the start of treatment and of serological parameters at 3 mo. These favorable results persisted until the end of the study. After a mean of 18 mo, a complete response had been achieved in 8 patients (73%) and a partial response in two patients. Proteinuria gradually decreased and had dropped significantly by 24 mo after the start of treatment. Adverse reactions to Tac treatment were not severe and were well tolerated. Although the blood levels of Tac in the participants ranged from 1.5 to 7.5 ng/mL, no definite relationship was noted between the efficacy of

the drug and its blood level. As the absorption profile of Tac showed some variations among the study patients, the appropriate blood levels and doses of Tac for young patients with lupus nephritis remains to be determined. Measuring the AUC of Tac in each patient is also needed to confirm whether its efficacy depends on its blood levels. Although further studies involving a larger number of patients, including a histological evaluation following Tac treatment, are needed, from our recent studies we believe that low-dose Tac, administered once daily, may be an effective and safe method for managing selected young patients with pediatric-onset, long-standing lupus nephritis<sup>[20,21]</sup>. Thus, Tac can be considered both effective and safe for adult and adolescent patients with SLE and lupus nephritis. However, Suzuki *et al*<sup>[37]</sup> recently reported that Tac treatment at current dose settings and usage has several limitations in efficacy for patients with severe active conditions. Thus, this controversy remains to be clarified in future studies. Table 1 shows recent published reports of calcineurin inhibitor therapy in pediatric-onset lupus nephritis.

## NEW MULTIDRUG THERAPY USING TACROLIMUS AND MIZORIBINE

Combination therapy consisting of two immunosuppressive agents with different modes of action is useful and frequently used for patients subjected to solid organ transplantation. The efficacy of multidrug therapy us-



ing MMF and Tac as induction therapy in patients with WHO class V + IV lupus nephritis has been reported<sup>[22]</sup>. This multidrug therapy resulted in less cytotoxicity than IVCY therapy; the authors concluded that multidrug therapy using MMF and Tac was superior to IVCY for inducing remission in their patients and was well tolerated. Lanata *et al.*<sup>[23]</sup> reported the usefulness of adding Tac to the MMF plus PDN regimen in 7 patients with diffuse proliferative lupus nephritis resistant to MMF and PDN, although clinical toxicity, such as ketoacidosis, infections and muscle pain, limited the use of this combination therapy. Since the mechanisms of action of MMF and Tac are probably complementary, these clinical observations suggested the potential usefulness of multidrug therapy to treat lupus nephritis. However, therapy-related adverse events remain a major therapeutic risk of the immunosuppressive treatment for patients with lupus nephritis.

The mode of action of MZR is very similar to that of MMF, that is, a selective inhibition of inosine monophosphate dehydrogenase in the *de novo* pathway of purine nucleotide synthesis. MZR inhibits T cell and B cell proliferation<sup>[41]</sup>. MZR reportedly exhibits relatively low clinical toxicity in patients with lupus nephritis<sup>[42,43]</sup>. Moreover, aside from its immunosuppressive effect, MZR also appears to have a beneficial effect against the adverse effects of calcineurin inhibitors, such as the CsA-induced intimal hyperplasia and perivascular inflammatory cell infiltration observed in rat models<sup>[44,45]</sup>. We have documented a significant suppression of intraglomerular and interstitial macrophage infiltration accompanied by significant suppression of chronicity indices following MZR treatment in patients with lupus nephritis<sup>[46]</sup>. Thus, we speculate that these histological observations may further support the use of MZR to treat selected patients with glomerular diseases, especially those treated with calcineurin inhibitors, such as CsA or Tac. Moreover, we hypothesized that combination therapy using low-dose Tac administered once-daily plus MZR instead of MMF, might be a useful alternative for the treatment of pediatric-onset refractory renal diseases including lupus nephritis<sup>[25,47]</sup>.

Next, we present a typical case of pediatric-onset lupus nephritis in which our novel multidrug therapy proved effective and safe<sup>[48]</sup>. The patient was a 14-year-old Japanese girl who was treated with PDN because of hemophagocytic syndrome that she had developed 6 mo earlier. When PDN was tapered, she developed malar rash, significant proteinuria and hematuria, hypocomplementemia and elevation of serum anti-dsDNA antibody titers. Percutaneous renal biopsy revealed International Society of Nephrology/Renal Pathology Society (ISN/RPS) class IIIa lupus nephritis (activity index, 8; chronicity index, 2). She was administered 2 courses of MPT followed by multidrug therapy consisting of Tac, MZR and PDN. Because she was of pubertal age, the PDN dose was reduced to a minimum at a relatively early stage. Her clinical and laboratory signs improved, and the sec-

ond renal biopsy performed 12 mo after the initial biopsy, revealed marked improvement to ISN/RPS class II lupus nephritis (activity index, 4; chronicity index, 1) without any significant increase in the number of chronic lesions. At present, 36 mo after the start of the administration of this therapy, she is free of SLE signs and symptoms without therapy-related clinical toxicity. Although the optimal treatment strategy for managing long-standing SLE, especially in pediatric patients, remains controversial, we believe that our treatment protocol is both effective and safe, and also easy to comply with for patients with pediatric-onset lupus. However, the long-term efficacy and safety of this regimen remains unclear. Further studies in a larger number of young patients with lupus nephritis are necessary to confirm the long-term efficacy and safety of our current protocol.

Further detailed studies involving a larger number of patients are needed to draw a conclusion. We believe that CsA, Tac and multidrug therapy including MZR are attractive treatments for young patients with lupus nephritis because of presumed less clinical toxicities than classical cytotoxic agents. Furthermore, MZR may attenuate histologic progression resulting from a suppressed accumulation of activated macrophages in the glomeruli and calcineurin inhibitor-related renal toxicities. From the view point of the balance between suppression of disease activity and the adverse effects of treatment, we believe that these treatments, including combination with MZR, may become the new treatment of choice for young patients with lupus nephritis.

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