Successful Treatment of Class IV+V Lupus Nephritis with Combination Therapy of High-dose Corticosteroids, Tacrolimus and Intravenous Cyclophosphamide

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Abstract

A substantial number of patients with lupus nephritis (LN) are refractory to conventional glucocorticoid (GC) treatment. Although many of these patients respond to immunosuppressive drugs such as intravenous cyclophosphamide (IVCY), azathioprine (AZA), mizoribine, tacrolimus, cyclosporine A (CSA) and mycophenolate mofetil (MMF), some remain refractory to such therapies. Recent studies of multi-target therapies have reported effective outcomes for immunosuppression following renal transplantation and refractory LN when therapy consists of two or more immunosuppressive drugs with different mechanisms of action. We herein report a case of LN unresponsive to IVCY that was successfully treated with the addition of tacrolimus and discuss the usefulness of multi-target therapy for LN.

Key words: tacrolimus, intravenous cyclophosphamide (IVCY), lupus nephritis (LN), immunosuppressive drugs, multi-target therapy

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Introduction

Although the prognosis of patients with lupus nephritis (LN) has improved in recent years owing to the use of aggressive immunosuppressive therapy, some cases of LN remain refractory (1). Most of these refractory patients are subsequently treated with standard glucocorticoid (GC) therapy but suffer from adverse effects of GCs such as osteoporosis and diabetes. In an effort to reduce the dose of GCs required in these therapies, immunosuppressive drugs are administered concomitantly, and, at present, the most popular immunosuppressive drug for treating LN is intravenous cyclophosphamide (IVCY) administered via either the NIH (2) or Euro Lupus regimen (3). Histopathological findings can provide useful information for optimizing the therapy and management of lupus nephritis (4, 5). Although IVCY combined with GCs has been shown to reduce the risk of end-stage renal failure, substantial adverse effects such as infections and bone marrow suppression are common. In addition, gonadal dysfunction and secondary malignancies are major concerns of long-term treatment with IVCY (6).

Several studies have suggested that improved efficacy with reduced overall adverse effects over IVCY alone can be achieved via combination therapy utilizing two or more immunosuppressive agents with different mechanisms of action (7-9).

Tacrolimus, an immunosuppressant developed in Japan, is used worldwide in the field of organ transplantation and was approved for use to treat LN in Japan in 2007. The efficacy of tacrolimus for LN was established in a randomized con-
trolled trial conducted in Japan (10) and confirmed in a system- 
tic review (11). In addition, tacrolimus has been re- 
ported to be safer than IVCY (12). We herein report a case 
of refractory LN that was successfully treated with a combi-
nation of tacrolimus and IVCY, despite neither of these 
agents demonstrating any efficacy when administered sepa-
rateley.

Table. Laboratory Data of the Patient on Admission

<table>
<thead>
<tr>
<th>Property (normal range)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (3,300-8,600/μL)</td>
<td>7,000</td>
</tr>
<tr>
<td>Lymphocyte (/μL)</td>
<td>456</td>
</tr>
<tr>
<td>Hb (13.2-17.2 g/dL)</td>
<td>12.5</td>
</tr>
<tr>
<td>Pt (129,000-329,000/μL)</td>
<td>230,000</td>
</tr>
<tr>
<td>TP (6.5-8.0 g/dL)</td>
<td>5.9</td>
</tr>
<tr>
<td>ALB (3.7-5.0 g/dL)</td>
<td>3.1</td>
</tr>
<tr>
<td>AST (5-38U/L)</td>
<td>25</td>
</tr>
<tr>
<td>ALT (4-43U/L)</td>
<td>16</td>
</tr>
<tr>
<td>BUN (5-22mg/dL)</td>
<td>26</td>
</tr>
<tr>
<td>Cr (0.3-1.0mg/dL)</td>
<td>0.9</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>63.9</td>
</tr>
<tr>
<td>Na (136-145mEq/L)</td>
<td>143</td>
</tr>
<tr>
<td>Cl (98-109mEq/L)</td>
<td>114</td>
</tr>
<tr>
<td>K (3.5-3.8mEq/L)</td>
<td>5.0</td>
</tr>
<tr>
<td>CRP (0.0-0.3mg/dL)</td>
<td>0.0</td>
</tr>
<tr>
<td>IgG (850-1,500 mg/dL)</td>
<td>803</td>
</tr>
<tr>
<td>IgA (140-240 mg/dL)</td>
<td>313</td>
</tr>
<tr>
<td>IgM (60-150 mg/dL)</td>
<td>178</td>
</tr>
<tr>
<td>C3 (90.0-140.0mg/dL)</td>
<td>60.3</td>
</tr>
<tr>
<td>C4 (18.0-30.0mg/dL)</td>
<td>7.3</td>
</tr>
<tr>
<td>CH50 (30.0-45.0 U/mL)</td>
<td>22.1</td>
</tr>
<tr>
<td>Anti DNA antibody (0-20 IU/mL)</td>
<td>57</td>
</tr>
<tr>
<td>Urine protein</td>
<td>3+, (4.7g/day)</td>
</tr>
<tr>
<td>Urine occult blood</td>
<td>2-</td>
</tr>
</tbody>
</table>

Case Report

In October 2004, a 17-year-old girl visited a local clinic 
complaining of joint pain in her right elbow. Although she 
was prescribed an antibiotic, the arthralgia did not improve, 
and a malar rash thereafter appeared. After visiting another 
hospital for a second opinion, physicians suspected systemic 
lupus erythematosus (SLE) due to the patient’s low white 
blood cell (WBC) count and facial erythema. In December, 
2004, she was admitted to our hospital with facial erythema, 
oral ulcers, arthritis and multiple small infarctions in the 
toes, likely due to vasculitis. She met many of the American 
College of Rheumatology’s revised criteria for the classifica-
tion of SLE by presenting with facial erythema, oral ulcers, 
arthritis, leukocytopenia, lymphopenia, proteinuria and the 
presence of anti-dsDNA antibodies (3,626 IU/mL) and anti-
nuclear antibodies (ANA). The serum complement levels of 
C3, C4 and CH50 were 58, 8.8 mg/dL and 13.9 U/mL, re- 
spectively, and a kidney biopsy revealed that the patient had 
class II LN according to the International Society of Neph-
rology (ISN)/Renal Pathology Society (RPS) 2003 crite-
ria (13, 14). Considering the risk for ovarian failure, we 
avoided the use of IVCY and instead treated the patient with 
a combination of 30 mg/day of prednisolone (PSL) (0.5 mg/ 
kg/day) and 150 mg/day of cyclosporine A (CSA), the ef-
cacy of which has been previously reported (15). After four 
weeks of this treatment, all of the patient’s LN signs and 
symptoms disappeared, and the dose of PSL was then ta-
pered to 10 mg/day over a three-month period.

In January 2007, the patient’s LN relapsed, and she pre-
sented with facial erythema, arthritis, proteinuria, an ele-
vated anti-dsDNA antibody titer (221 IU/mL) and relatively 
low serum complement levels (C3, 81.2 mg/dL; C4, 7.8 mg/ 
dl; CH50, 24.1 U/mL). Because she refused to increase the 
dose of PSL, we continued PSL at 10 mg/day and substi-
In January 2010, the patient was admitted to our hospital due to worsening of nephrotic syndrome caused by LN. In a physical examination performed on admission, the patient’s weight was 72 kg and her height was 157 cm. She presented with facial erythema, severe leg edema, a weight gain of more than 10 kg in three months and a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 16. Her laboratory data on admission are shown in the Table. A renal biopsy was performed and 26 glomeruli were obtained, two of which exhibited sclerosed glomeruli and five of which demonstrated cellular crescents. Spiking of the glomerular basement membranes was present. Marked mesangial proliferation and segmental endocapillary proliferation were observed in most glomeruli. Thickening of the glomerular capillary walls was also present. There was mild lymphoid cell infiltration in the interstitium. The biopsy specimen disclosed diffuse proliferative LN with membranous glomerulonephritis and lobular accentuation (class IV-S (A/C) + V; Fig. 2). Immunofluorescent staining of the renal biopsy specimen was positive for IgG, C3 and C4 (Fig. 3).

The dose of PSL was increased to 60 mg/day (1.0 mg/kg/day) and IV CY (500 mg, biweekly) treatment was initiated.

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Figure 2. Periodic acid-Schiff (PAS) staining and periodic acid-methenamine silver (PAM) staining of the renal biopsy specimen. Note the presence of marked mesangial matrix deposition and cell proliferation. The glomerular capillary walls are thickened (PAS; 400×). PAM stain highlights the spiking of the glomerular basement membranes (1,000×).

Figure 3. Immunofluorescent staining of the renal biopsy specimen. Abundant deposits of IgG, C3 and C4 are noted in the glomerular capillary and partially in the mesangium.
Despite increasing the dose of IVCY to 700 mg from the third infusion, low serum complement levels (C3 61.9 mg/dL, C4 7.6 mg/dL) and severe proteinuria persisted. Since the patient’s LN was not effectively treated with the administration of a single immunosuppressive drug with PSL, we chose to begin multi-target immunosuppressive therapy, including the combination of IVCY and CSA (17). As the patient refused to take CSA again because of the smell of the drug, we began adding 3 mg/day of tacrolimus to PSL+IVCY therapy. In addition, because the patient’s blood pressure control was insufficient, irbesartan (100 mg/day), an angiotensin receptor blocking agent, was administered simultaneously. Two weeks after the commencement of the combination therapy, the patient’s proteinuria decreased from 4+ (6.02 g/day) to 2+ (1.38 g/day), while the C3, C4 and CH50 serum levels increased to 78.6, 27.7 mg/dL and 40.6 U/mL, respectively. After completing the 6th course of IVCY in June 2010, the patient was discharged with no leg edema, mild proteinuria (1+, 1.10 g/day) and a negative status for anti-dsDNA antibodies. One year after discharge, the patient continues to take 9 mg/day of PSL and 2 mg/day of tacrolimus without either proteinuria or any other active LN signs (Fig. 4).

Discussion

While the general prognosis of LN has improved since the introduction of GC and immunosuppressive drugs such as IVCY some cases still remain refractory, and these compounds, including IVCY and azathioprine, have substantial toxic effects (6). In recent years, mycophenolate mofetil (MMF) has been shown to be the most effective therapeutic agent against LN, not only in maintenance therapy (18, 19), but also in remission-induction therapy (20, 21). However, at present, MMF has not been approved to treat LN in Japan. Mizoribine, another inosine 5’-monophosphate (IMP) dehydrogenase inhibitor similar to MMF is expected to be effective for LN. However, as tacrolimus was found to be superior to mizoribine in a randomized study in patients with rheumatoid arthritis (22), mizoribine (50 mg three a day orally) is usually ineffective for LN. Recently, mizoribine pulse therapy was introduced to raise the peak concentration of the drug, which has shown some efficacy and tolerability (16); however, this strategy is not approved in general. CSA, another calcineurin inhibitor similar to tacrolimus, has been reported to be effective for treating refractory LN (15, 17); however, it is also not approved for use in LN patients in Japan. Therefore, at present, tacrolimus may be one of the best therapeutic agents against LN available in Japan. Indeed, recent reports have shown tacrolimus and MMF to be similarly effective for remission induction in the treatment of LN (23), particularly membranous LN (24). Furthermore, a randomized trial demonstrated that induction therapy for LN with tacrolimus is as efficacious as IVCY and has a more favorable safety profile (25).

At the patient’s relapse, we initially did not increase the dose of PSL according to the patient’s request, and immunosuppressive therapy was added to the baseline PSL treatment, as CSA, mizoribine, a combination of mizoribine plus tacrolimus and IVCY alone did not improve the LN. High-dose PSL may have been effective for treating the first relapse of LN in this patient. However, increasing the doses of PSL (60 mg/day) and IVCY did not achieve any significant improvements for the second relapse. As decreasing
proteinuria in patients with membranous LN takes a long time, if we had observed the patient longer, her proteinuria might have improved. However, Sloan et al. (26) reported the remission rate of patients with class IV + V with cyclophosphamide to be only 21% after 2.7 years of follow-up, and Zhang et al. (27) reported the complete remission rate to be 21.1% after six months of induction therapy with tacrolimus of class IV + V LN. Hence, this subtype may be refractory to usual immunosuppressive therapies such as IVCY or tacrolimus. Therefore, we decided to treat the patient with combination therapy of tacrolimus and IVCY. The effectiveness of this combination therapy may result from the different mechanisms of action of these two agents on immune cells. Specifically, IVCY inhibits antibody production by B-cells and antigen presentation to T-cells by antigen-presenting cells such as B-cells and dendritic cells, while tacrolimus reduces cytokine production by suppressing the T-cell function. In addition, tacrolimus functions similar to CSA in reducing proteinuria by stabilizing the actin cytoskeleton of kidney podocytes (28). The other mechanism of tacrolimus depends on its inhibitory effects on P-glycoprotein, which accelerate to excrete concomitant drugs from the inside of cells. Therefore, tacrolimus can restore the intracellular therapeutic levels of corticosteroids, thereby leading to the improvement of LN (29). A previous study showed that treatment with angiotensin receptor blockers reduces proteinuria in conjunction with immunosuppressive therapy in patients with LN (30). In our case, irbesartan might have also partially contributed to improving the proteinuria. Given that this type of multi-target therapy has been reported to be effective for treating LN (7), IVCY plus tacrolimus may represent a promising therapeutic option for refractory LN, although further studies are needed to confirm its efficacy and safety.

The authors state that they have no Conflict of Interest (COI).

References


