Concise Report

The difference between lupus nephritis class IV-G and IV-S in Koreans: focus on the response to cyclophosphamide induction treatment

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Objectives. To evaluate the response to induction therapy with intravenous (IV) cyclophosphamide (CYC) in Korean patients with class IV-G (diffuse global proliferative glomerulonephritis) and class IV-S (diffuse segmental proliferative glomerulonephritis) lupus nephritis (LN) according to the classification system of the International Society of Nephrology/Renal Pathology Society (ISN/RPS).

Methods. Of the 52 patients with biopsy-proven diffuse proliferative LN, who had been treated with IV CYC over a 10-yr period, 42 had been treated with IV CYC (equal to or more than 500 mg) for 6 consecutive months and had biopsy specimens containing more than nine glomeruli. The renal pathology of these 42 patients was reclassified according to the International Society of Nephrology and the Renal Pathology Society 2003 classification, and their renal response rates and laboratory indices after induction therapy were analysed. Results. Of the 42 patients assessed, 30 (71%) had IV-G and 12 (29%) had IV-S. Pre-treatment 24 h urinary protein was significantly higher in class IV-G than in class IV-S LN. Following induction therapy, complete remission rates were significantly higher in patients with IV-S (67%, 8/12) than in patients with IV-G (33%, 10/30) LN. Conclusions. Class IV-G LN responded more poorly to induction therapy with IV CYC pulse than class IV-S LN.

KEY WORDS: Lupus nephritis, Cyclophosphamide, Remission induction.

Introduction

The clinical presentation of lupus nephritis (LN) is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis, and the occurrence of kidney disease is the most important predictor of morbidity and mortality in patients with SLE [1].

One of the standard treatments for severe lupus glomerulonephritis is an intravenous (IV) pulse of cyclophosphamide (CYC) [2]. This therapy, however, has been associated with potentially severe toxicities, including premature gonadal failure, bone marrow suppression and opportunistic infection, thus limiting its prolonged use [3]. The newer biological agents such as rituximab, abatacept and monoclonal antibodies are in current clinical trials as effective alternatives to CYC, with fewer adverse effects for patients with diffuse proliferative LN [4, 5].

In 1974, the World Health Organization (WHO) classified the histopathology of LN according to distinctive patterns of injury, with revisions in 1982 and 1995. To accommodate recent clinicopathological findings and eliminate inconsistencies and ambiguities, the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) recently proposed a new classification of LN [6], which provides clear definitions of diagnostic categories based on quantitative assessment of individual histological lesions. In particular, class IV LN was reclassified as a global form [diffuse global proliferative glomerulonephritis (IV-G)] or a segmental form [diffuse segmental proliferative glomerulonephritis (IV-S)] based on capillary tuft involvement.

The distinction between IV-S and IV-G may have important implications for differences in pathogenesis and outcomes. However, although several retrospective studies have shown significant clinical and morphological differences between IV-G and IV-S LN, no significant differences in outcomes were detected [7, 8]. We have therefore assessed the clinical features of Korean patients with IV-G and IV-S LN and their response to IV CYC pulse induction therapy.

Patients and methods

Patients

The records of 52 patients with class IV LN who were admitted to one tertiary hospital from 1997 to 2006 were retrospectively reviewed. All patients fulfilled the 1982 American Rheumatism Association criteria for the classification of SLE [9] and the kidney lesions were classified using the original WHO classification of LN (1974) [10]. Of these 52 patients, 42 with kidney biopsy specimens containing more than nine glomeruli and who completed induction treatment with IV CYC (≥500 mg/month) for 6 consecutive months were recruited. The study protocol was approved by the institutional review board of Asan Medical Center.

All patients were treated with methylprednisolone (0.5–1.0 mg/kg/day or equivalent) for 4–6 weeks, after which the amount was tapered slowly to a maintenance dose (5–10 mg/day). An experienced pathologist who had no information about the clinical outcomes of the patients reviewed the biopsy specimens. The diffuse glomerular lesions were reclassified using the ISN/RPS classification system. Patients with lesions showing involvement of ≥50% of the glomerular tufts were classified as IV-G, whereas those with segmental lesions affecting <50% of the glomerular tufts were classified as IV-S.

Data collection

Demographic data (sex, age and duration of disease), clinical data (CYC dose, methylprednisolone dose and blood pressure), autoantibody profiles (anti-dsDNA, anti-nuclear, anti-Sm, antiENA), follow-up data and adverse effects were recorded. The results of the second biopsy were used to determine the renal response rate following induction therapy. Complete remission was defined as the absence of proteinuria and urinary casts for at least 6 months following induction therapy.

Patients treated for severe lupus glomerulonephritis (IV-G) or a segmental form (IV-S) based on capillary tuft involvement.
anti-nucleic protein, anti-Ro/La, anti-β2-glycoprotein I and anti-cardiolipin antibodies and lupus anticoagulants) and biochemical parameters [white blood cells, and haemoglobin; creatinine, albumin and complement (C); 24 h proteinuria; and glomerular filtration rate (GFR)] and SLEDAI [11] at the time of kidney biopsy were obtained from the patient records. Biochemical parameters, SLEDAI scores and anti-dsDNA antibody concentration were compared before and after treatment, and between IV-G and IV-S patients. Activity indices (AIs) and chronicity indices (CIs) were calculated (maximum scores, 24 for AI and 12 for CI) and interstitial fibrosis was evaluated for each biopsy specimen that was graded semi-quantitatively using a scoring system from 0 to 3 (0 = no changes, 1 = mild, 2 = moderate, 3 = severe) [12].

**Definition of treatment response**

Complete remission (CR) was defined as a serum creatinine concentration <1.4 mg/dl, proteinuria <500 mg/day or trace by dipstick, the absence of active sediment [<10 red blood cells/high power field (RBC/HPF)] and no casts. Partial remission (PR) was defined as a serum creatinine concentration <1.4 mg/dl, proteinuria decreased by 50% from baseline or 1+ to 2+ by dipstick. No response (NR) was defined as a deterioration of renal function exclusive of other causes (such as sepsis or nephrotoxic agents), or a reduction in proteinuria with failure to reach PR or persistence of active urinary casts (>10 RBC/HPF).

**Statistical analysis**

All values were expressed as mean ± s.d. Responses to treatment were compared by the Pearson chi-square test. Continuous variables were compared using the Mann–Whitney U-test, whereas categorical variables were compared using the chi-square test or Fisher’s exact test. All statistical evaluations were performed using the SPSS program, version 12.0 (SPSS, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

**Results**

**Clinical data and baseline parameters**

Of the 52 patients (48 women and 4 men), 42 (38 women and 4 men) met each of the criteria for study inclusion. Among the excluded patients, three (two IV-G and one IV-S) did not complete 6 consecutive months of CYC therapy, two (both IV-G) were treated with a lower dose of IV CYC pulse (<500 mg), and five (three IV-G and two IV-S) had inadequate biopsy specimens.

Of the 42 patients assessed, 30 (71%) had IV-G, and 12 (29%) had IV-S. The cumulative doses of CYC and prednisolone did not differ between the IV-G and IV-S groups, nor did the pathological profiles including glomerular sclerosis, cellular crescent, interstitial fibrosis and AI/CI of biopsy specimens. Justly, the IV-S group had predominantly segmental endocapillary proliferation and the IV-G group had predominantly global endocapillary proliferation.

Prior to treatment, the 24 h urinary protein level was significantly higher in the IV-G than in the IV-S group, whereas the anti-dsDNA concentration was significantly lower in IV-G than in IV-S patients. The serological profiles, including autoantibodies (data not shown), GFR and serum concentrations of albumin, creatinine and C3/C4, did not differ between the IV-G and IV-S groups. At the time of renal biopsy, 15 patients (11 IV-G, 4 IV-S) were hypertensive (blood pressure $\geq 140/90$ mmHg) (Table 1).

**Response to CYC**

After six doses of IV CYC, 18 patients (10 IV-G and 8 IV-S) achieved CR, 18 (15 IV-G and 3 IV-S) achieved PR and 6 (5 IV-G and 1 IV-S) showed NR. The CR rate after 6 months of IV CYC treatment was significantly higher in IV-S (67%, 8/12) than in IV-G (33%, 10/30) patients ($P < 0.05$).

After six doses of IV CYC, both GFR and 24 h urinary protein excretion improved significantly in the IV-G group. In the IV-S group, however, 24 h urinary protein excretion improved significantly, while the changes in GFR did not reach statistical significance (Fig. 1). In both the groups, serum concentrations of albumin (IV-G: 2.7 ± 0.5 g/dl, IV-S: 3.8 ± 0.3 g/dl) and complement components C3 (IV-G: 82.3 ± 17.7 mg/dl, IV-S: 88.1 ± 21.8 mg/dl) and C4 (IV-G: 16.9 ± 9.5 mg/dl, IV-S: 19.2 ± 8.2 mg/dl) increased significantly, whereas anti-dsDNA level (IV-G: 36.5 ± 33.4 U/ml, IV-S: 55.7 ± 44.4 U/ml) decreased significantly.

To see the late response, the data of 1-yr proteinuria were evaluated from 31 patients (23 of IV-G, 8 of IV-S). There was no significant change between 1-yr and 6-month proteinuria in both the groups.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>IV-G (n = 30)</th>
<th>IV-S (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.1 ± 7.8</td>
<td>32.7 ± 9.7</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Female (n (%))</td>
<td>27 (90)</td>
<td>11 (82)</td>
<td>0.57</td>
</tr>
<tr>
<td>Duration of SLE (months)</td>
<td>26.4 ± 30.0</td>
<td>43.2 ± 50.4</td>
<td>0.38</td>
</tr>
<tr>
<td>CYC cumulative dose (g)</td>
<td>5.1 ± 1.5</td>
<td>6.0 ± 0.8</td>
<td>0.10</td>
</tr>
<tr>
<td>PD cumulative dose (g)</td>
<td>6.9 ± 4.2</td>
<td>6.8 ± 3.9</td>
<td>0.99</td>
</tr>
<tr>
<td>WBC ($\times 10^3$)</td>
<td>6.2 ± 4.5</td>
<td>6.1 ± 3.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Hb (g/l)</td>
<td>10.1 ± 1.6</td>
<td>10.6 ± 1.6</td>
<td>0.50</td>
</tr>
<tr>
<td>HTN (BP $\geq 140/90$ mmHg), n (%)</td>
<td>11 (37)</td>
<td>4 (33)</td>
<td>0.84</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>77.4 ± 17.2</td>
<td>85.9 ± 25.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.3 ± 0.6</td>
<td>2.7 ± 0.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>5.1 ± 3.0</td>
<td>2.3 ± 1.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>50.8 ± 20.6</td>
<td>48.3 ± 18.4</td>
<td>0.80</td>
</tr>
<tr>
<td>C4 (mg/dl)</td>
<td>10.2 ± 5.8</td>
<td>10.8 ± 7.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Anti-dsDNA antibody titre (U/ml)</td>
<td>804.2 ± 385.4</td>
<td>1295.2 ± 603.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. *Values expressed as median percentage (minimum–maximum). PD, prednisolone; WBC, white blood cells; Hb, haemoglobin; HTN, hypertension.
To see the long-term prognosis, we evaluated the serial changes of GFR from 23 patients (14 of IV-G, 7 of IV-S) for 5yrs and compared data between 6-month and 5-yr proteinuria. In the IV-G group, there was a significant decline of GFR (94.3 ± 25.4 ml/min vs 72.5 ± 33.2 ml/min); however, in the IV-S group, the decline of GFR was not statistically significant (94.2 ± 27.6 ml/min vs 86.0 ± 33.0 ml/min) (Fig. 2). The relapse rates of IV-G and IV-S were 30% (3/10) and 13% (1/8) during follow-up period (median 50 months).

Discussion
This retrospective evaluation is noteworthy in that it demonstrated differences in response to CYC induction therapy as well as in initial clinical features between class IV-G and IV-S groups. However, our results somewhat differed from those of the LN collaborative group who showed that category III lesions in 50% or more of glomeruli had poorer prognosis than that of category IV disease according to the 1982 WHO classification, which formed the rationale for the revision of the WHO classification in 2003 [13]. The differences might have been caused mainly by the diversity of the regimens. Our regimens included just a monthly IV 500 mg/month CYC for at least 6 months since an adequate dose of CYC (≥500 mg/month) has been shown to influence patient outcome [14]. In addition, we assessed relatively short-term outcomes rather than long-term outcomes since we first wanted to test the response to CYC induction therapy.

We found that the overall CR rate to induction therapy among patients with class IV LN was 43%, similar to that in other Asian populations [1, 15]. In contrast, the CR rate after IV pulse CYC (six pulses in 24 weeks) was 9.5% in Caucasian patients with proliferative LN [16]. This discrepancy may be related to differences in ethnicity or to different severity of renal disease at biopsy.

There is a strong association between diffuse proliferative glomerulonephritis and the level of anti ds-DNA antibodies, and an association between the serum concentration of complement components and disease activity. Prior to treatment, the serum concentrations of C3 and C4 did not differ between IV-G and IV-S patients, whereas the concentrations of anti-ds-DNA antibodies were significantly lower in the IV-G than in the IV-S group. Other studies have reported that pre-treatment serum concentrations of C4 [7] and C3 [17] were lower in IV-S than in IV-G patients, and IV-G patients have been reported to have higher [17] or equivalent [13] concentrations of anti-ds-DNA antibodies when compared with IV-S. This lack of consensus indicates the need for studies in larger numbers of patients.

The poor response of patients with IV-G LN to IV CYC induction therapy may be related to their initial level of 24 h urinary protein. Since proteinuria affects remission, patients with IV-G LN were at a disadvantage for achieving CR. Nevertheless, achieving CR was important because those patients who achieved CR to initial CYC treatment were less likely to develop renal flares and end-stage renal failures than patients who achieved PR [15, 18].

There were several reports about histological differences between two subgroups. Biopsies from IV-G LN patients were dominated by overall immune and hyaline deposits, whereas biopsies from IV-S LN patients showed a dominance of mesangial deposits and a much higher rate of glomerular fibrinoid necrosis [17]. These histological differences suggest that IV-S and IV-G LN patients may have different prognoses or different responses to CYC. To our knowledge, however, since the classification by the ISN/RPS, there has been no report showing significantly different outcomes between IV-S and IV-G patient groups. Since histological chronicity score and cumulative dose of CYC have been reported to be predictors of CR [15, 18], the different outcomes observed in previous studies [8, 13, 17] might have resulted from differences in these predictors.

Our study had several limitations, including its retrospective design and its assessment of a small number of patients at a single centre. Furthermore, the 10 excluded patients may have affected our results. And there was a possibility that a less aggressive CYC regimen might have led to a lower CR in 6 months. Nevertheless, we have shown differences in initial presentation and CR to IV CYC induction between patients with IV-G and IV-S LN. Our findings suggest that induction therapy with an immunosuppressant other than CYC might be considered for IV-G LN patients.
Disclosure statement: The authors have declared no conflicts of interest.

References