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Immunoadsorption Plasmapheresis in Patients with Lupus Nephritis

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Object

In addition to the use of steroids and immunosuppressants as a treatment for SLE, it is also theoretically useful to eliminate positively blood anti-DNA antibodies and their immune complexes by plasmapheresis[1] and this has become a treatment method which could not be ignored. However, its effects and procedures have not been established. Anti-DNA antibodies are capable of cross-reacting with anionic compounds. In recent years, an immunoadsorption therapy using dextran phosphate with an anionic compound as a ligand has been developed and applied clinically.[2] In this study, we conducted immunoadsorption in patients with lupus nephritis using an immunoadsorption column, SL-01 (Selesorb, Kaneka Corporation) to evaluate its elimination effects on various autoantibodies and immune complexes as well as to compare the results with those obtained by double filtration plasmapheresis (DFPP).

Subjects

Twenty-eight patients with SLE nephritis were included who satisfied ARA standard criteria and had not been given an increased dose of steroid over a period exceeding 1 month before the start of the elimination therapy. Immunoadsorption was carried out in 14 patients with a mean age of 37.6 years who were given a mean dosage of 22.5 mg/day of steroid. DFPP was conducted in 14 patients with mean age 34.6 years who were given a mean steroid dosage of 15 mg/day. In the patients given immunoadsorption therapy, the mean 24-hr creatinine clearance and the mean IgG level were as high as 19 ml/min and 200 mg/dl, respectively, while other parameters including urinary protein excretion, anti-DNA antibodies and C3 showed similar values for both groups.

Methods

In the immunoadsorption method, after separating plasma by a membrane separator (FS-08, Kaneka Corporation), the plasma was introduced to a SL-01 column and processed by 3-liter adsorption. In DFPP, the plasma separated by a membrane separator was introduced to the secondary filter (Evaflax3A, Kurare) to eliminate pathogenetic factors.

Plasma processing was conducted once in both the adsorption and DFPP groups and the following parameters were measured before and after the treatment after 1 and 2 weeks and after 1, 2 and 3 months; anti-DNA antibodies, anticardiolipin antibodies, immune complexes, complements, immunoglobulins, lymphocyte subsets, daily urinary protein excretion, and 24-hr creatinine clearance. The following formula was used to calculate the elimination rates before and after the therapies.

$$\text{Elimination rate} = \frac{\text{Pretreatment level} - \text{Posttreatment level}}{\text{Pretreatment level}} \times 100.$$

Results

1. Capacity to eliminate pathogenetic factors by SL-01. The mean values before and after the adsorption and the elimination rate were 21.0, 11.4 and 44.8% for anti-DNA antibodies; 18.4, 14.8 and 32.1% for anti-ssDNA antibodies; and 2.2, 1.7 and 39.6% for anti-dsDNA antibodies and significant decreases were shown for all the parameters. The mean values before and after the adsorption and the elimination rate for anticardiolipin antibodies were 1.5, 0.9 and 37.3% indicating a drop. Significant drops after the adsorption were also shown for all the cases of Clq-IC and C3d-IC and the mean elimination rates were 44.2 and 47.8%, respectively. The mean elimination rates for IgG, IgA and IgM were 9.9, 11.7 and 20.0%, respectively, and they were all decreased significantly after the adsorption.

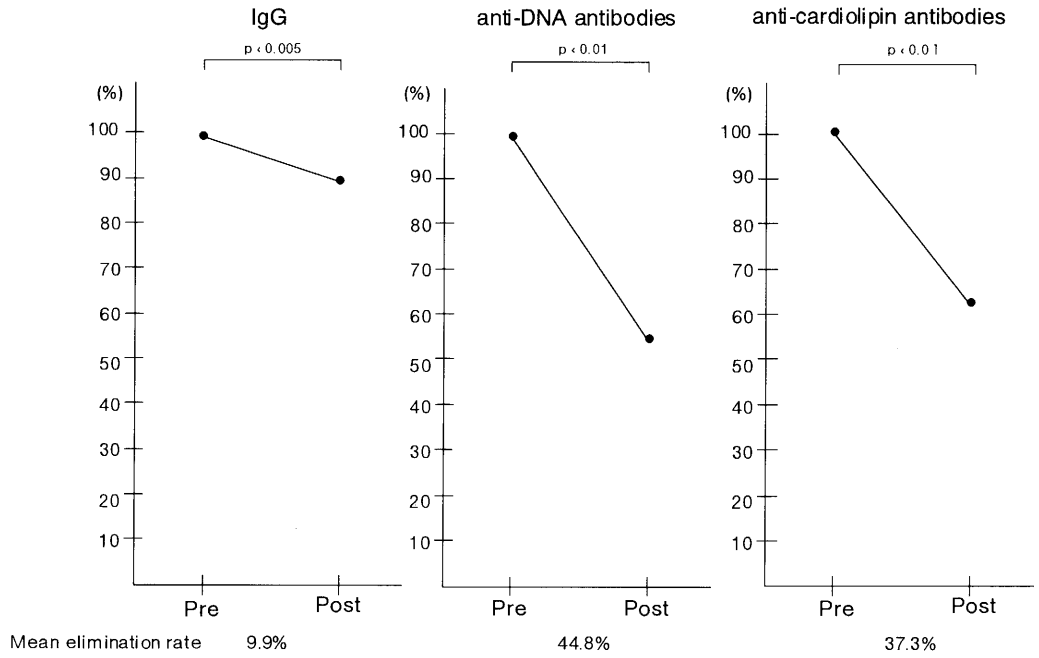

Fig. 1 Changes in IgG, anti-DNA antibody and anti-cardiolipin antibody levels after adsorption by SL-01 by setting the preadsorption values as 100%.

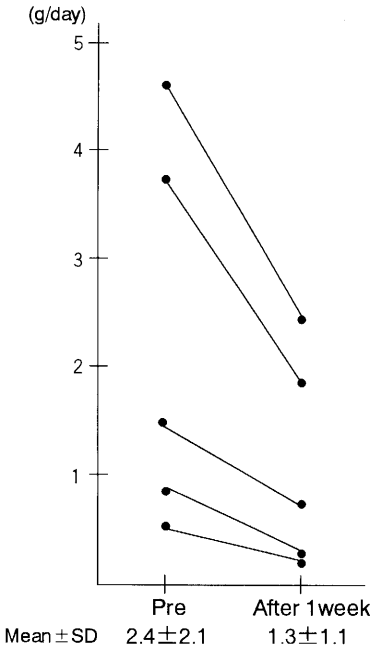

Fig. 2 Changes in 24-hour urinary protein excretion.

When the preadsorption values for IgG, anti-DNA antibodies and anti-cardiolipin antibodies were set at 100% and the postadsorption values were expressed as a percent of the preadsorption values, the elimination rates for anti-DNA and anti-cardiolipin antibodies were more selectively compared to IgG (Fig. 1). Changes in daily urinary protein excretion before and 1 week after the adsorption are shown in Fig. 2. Although the urinary protein amount 1 week after the adsorption was measurable only in 5 cases, the amounts decreased to a half in all of them.

2. Comparison of time-course changes in the adsorption therapy and DFPP. The mean elimination rates of anti-DNA antibodies immediately after the adsorption and DFPP were 44.8% and 69.1%, respectively. The recovered to the pretreatment value after 1 week in the adsorption group whereas the decreasing tendency continued until 1 month later in DFPP group. Anti-cardiolipin antibody level decreased significantly after the adsorption but recovered to the pretreatment value after 1 week. The mean elimination rate for IgG immediately after treatment was 9.9% by adsorption and 43.6% by DFPP. Although a slight increase was observed after 1 week of the adsorption compared to the pretreatment value, it was not significant, and an increase was shown for 2 weeks after DFPP and a decreasing tendency was observed after 2 months. While a decrease in CD4+ was reported for SLE,[3,4] the number of cases with the values below the standard was 4 by adsorption therapy and 1 by DFPP. The time-course change was absent after adsorption therapy whereas DFPP indicated significant increases after 1 week, 1 month and 2 months. Neither the adsorption nor DFPP showed a significant difference for CD8+ cells. Time-course change in the CD4/CD8 ratio was absent after the adsorption while it decreased immediately after DFPP and increasing tendency was observed after 1 week compared to the pretreatment value.

T lymphocytes were analysed by two-color flow cytometry to examine changes by apheresis. While it has been reported that the decreased

CD4+/2H4+ suppressor inducer T cells seen in the SLE patients were increased significantly after 8 weeks of the plasmapheresis,[5] no significant change in these cells was observed in all the cases given the adsorption therapy by the examination up to 1 month and changes were absent in 4 cases indicating values below the standard. A decreasing tendency was shown immediately after DFPP but examination was not conducted thereafter.

CD8+/CD11b+ suppressor T cells did not show any change in any case both after the adsorption and DFPP; in 6 patients in the adsorption group and in 10 patients in the DFPP group, in which the values were below the standard, significant increases were shown immediately after the therapies but significant changes were absent thereafter.

No significant change was observed for CD4+/2H4− helper T cells or CD8+/CD11b− cytotoxic T cells.

Effects on proteinuria after 1 month of the therapies were judged as improved when a decrease exceeding 30% compared to the pretreatment value was shown and aggravated when an increase exceeding 30% was shown: 2 out of 8 cases of the adsorption group were improved, 5 were unchanged and 1 was aggravated while 3 out of 7 cases of the DFPP group were improved, 4 were unchanged and none were aggravated. Change in creatinine clearance before and 1 month after the therapy were varied in the adsorption group but the values were all increased in the DFPP group with a mean improvement of 19.7 ml/min.

Discussion

Differing from plasmapheresis, immunoadsorption does not require plasma preparation for substitution and, moreover, is superior in that it can eliminate pathogenetic factors selectively. SL-01 is a newly developed immunoadsorbent using dextran sulphate as a ligand. In the results of the present study, elimination rates for anti-DNA antibodies and anti-cardiolipin antibodies were higher than those for various immunoglobulins including IgG suggesting a more selective adsorption as described in other reports.[6,7]

By DFPP, a prolonged suppression of anti-DNA antibodies and IgG was shown in comparison to the adsorption therapy. It was considered possible that the effects of DFPP were modified by elimination of various fluid factors such as cytokines related to inflammatory reactions or immunoresponses in addition to the elimination of anti-DNA antibodies and immune complexes. We assessed the clinical effects in terms of proteinuria and renal functions because clinical symptoms of SLE were scarce except nephropathy; the majority of the patients did not show any change in proteinuria after 1 month of therapy. However, urinary protein excretion decreased to about a half after 1 week of the adsorption therapy probably due to the effects of adsorption therapy. While the superiority of the present therapy in selective elimination of various autoantibodies and immune complexes was demonstrated, the therapy was inferior in terms of the amounts eliminated.

References

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