Intravenous Immunoglobulin (IVIg) Therapy in MPO-ANCA Related Polyangiitis with Rapidly Progressive Glomerulonephritis in Japan

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SUMMARY: For 30 myeloperoxidase (MPO) antineutrophil cytoplasmic antibody (ANCA) related rapidly progressive glomerulonephritis patients (male 17, female 13, average age of 68 ± 11.8 years old), intravenous immunoglobulin (IVIg) (400 mg/kg/day) was administered for 5 consecutive days before or along with conventional immunosuppressive therapy in Japan. Twenty patients were treated with IVIg before the start or newly increase of conventional therapy and evaluated the independent effect of this therapy. In these patients, just after IVIg, significant decrease of CRP from 8.61 ± 5.77 to 5.47 ± 4.50 mg/dl (P < 0.001) was noted with improvement of elevated serum creatinine in 12 out of 19 patients (63%). In the analysis of the overall outcome of 30 patients, at 3 months after IVIg and following conventional therapy, no patients showed renal death except 4 for whom hemodialysis had been started before IVIg. At 6 months, renal survival rate were 92% (newly renal death 2 out of 26) and 2 patients died due to cerebral bleeding (survival rate was 93%). No fatal infection was noted. IVIg might be the potent inducible therapy which can be promoted before the beginning of conventional immunosuppressant treatment for relatively aged and lower immunopotent MPO-ANCA patients in Japan.

Rapidly progressive glomerulonephritis (RPGN) is often associated with systemic vasculitis presenting antineutrophil cytoplasmic antibody (ANCA) (1). These ANCA-related RPGN often necessitate aggressive immunosuppressive treatment using high dose corticosteroid and cyclophosphamide (CYC) which sometimes brought about severe side effects especially sometime fatal infections, since these diseases often occur in relatively aged populations. To avoid these fatal side effects, intravenous immunoglobulin (IVIg) therapy has been utilized in Europe for these ANCA-related vasculitis and has been proved to be clinically safe, suppress disease activity for at least 1 year, and reduce the total dose of immunosuppressive agents (2-4). Although these reports of this therapy are useful, it is necessary to be prudent for the direct application of these results for those in Japan because in Europe, the distribution of the type of disease tends to orient to Wegener’s granulomatosis (WG) which are not so frequently experienced as the causative disease of RPGN in Japan. Recent survey for the incidence of RPGN in Japan revealed that 62% of 593 RPGN patients from 1996 to 2000 were MPO-ANCA positive, in contrast to only 4% of PR3-ANCA positive patients (5). Therefore, the independent survey is necessary to prove the efficacy of this therapy as the safe and potent induction therapy for MPO-ANCA related RPGN.

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Patients and methods: Patients: Thirty MPO-ANCA related RPGN patients (male 17, female 13) in Japan were treated with IVIg before or during the conventional immunosuppressant therapy using corticosteroid and CYC. These patients were treated in 5 hospitals (Kitano Hospital: 12 cases, Ehime Prefecture Hospital: 8, Osaka University Hospital: 4, Tsukuba University Hospital: 4 Kyoto University Hospital: 4) in Japan separately from 2001 to 2003. Average age of the patients was 68 ± 11.8 from 36 to 83 years old. All patients showed elevated serum MPO-ANCA as well as characteristic pathology observed in the renal biopsy specimen. All patients were provided written informed consent for renal biopsy and the present treatment protocol.

Treatment protocol: For all patients except one, IVIg was administered intravenously once for 5 consecutive days (400 mg/kg/day) (Kenketus Venilon-I, Teijin Co., Ltd., Tokyo, or Kenketsu Glovenin-I, Nihon Pharmaceutical Co., Ltd., Tokyo, Japan ). One patient was treated with IVIg twice during her hospital course. Twenty patients (male 12, female 8, average age: 71.3 ± 8.82) were treated with IVIg before the start or newly increase of conventional immunosuppressive therapy and the effect of the IVIg could be evaluated independently.

Clinical features before IVIg treatment: All patients showed elevation of creatinine (Cre) before IVIg with mean value of 4.04 ± 2.94 mg. Twenty-one of them were diagnosed RPGN with rapid increase of Cre more than double within 3 months before entry. For four patients, hemodialysis had to be started before IVIg therapy. The activity of the inflammation were severe with the mean CRP of 7.2 ± 5.5 mg/dl. All patients were MPO-ANCA positive with 243.7 ± 355.2 EU.

These patients were under various complicated diseases prior to the burst of MPO-ANCA disease. Ten cases showed one or more pulmonary diseases such as pulmonary fibrosis: 7 cases, latent tuberculosis: 2, aspergilosis: 1, other bacterial infections: 3. Other complications were as follows: Idiopathic thrombocytic purpura 3, hepatitis B virus carrier 2, diabetes mellitus 2, aortic aneurysm 1, mononeuropathy 1, malignancy 1 (laryngeal cancer). In addition, 2 patients were MRSA carrier.

RESULTS

Response to the IVIg therapy: For 20 patients independently treated with IVIg before the start or the increase of the immunosuppressants, the evaluation of the response to this therapy was performed separately within 14 days for 19 out of 20 patients whose data just after the IVIg were available. The significant decrease of the CRP was noted just after the IVIg from 8.61 ± 5.77 to 5.47 ± 4.50 mg/dl (P < 0.001). Although the average level of Cre did not show a significant decrease within such short period of observation (from 3.46 ± 2.34 to 3.39 ± 2.16 mg/dl P.n.s.), it was noteworthy that the elevation of Cre before IVIg stopped in one and rather decreased in 12 patients.

The evaluation of the effect of IVIg on MPO-ANCA titers was available in 13 of 19 patients. There was no significant decrease of these titers just after the IVIg (from 253.30 ± 275.40 to 410.07 ± 621.56 EU).

Outcome of the patients: Following or along with IVIg, patients were treated with conventional immunosuppressants including corticosteroid. Two out of 30 patients did not need to add additional therapy after IVIg. For other 28 patients, average initial dose of 33.4 ± 11.2 mg of Prednisolone (0.6 ± 0.1 mg/kg/day) were administered. For those without complicated infectious diseases, pulse therapy of methylprednisolone (0.5-1 g/day for 3 days) were performed in 8 and oral CYC 50 mg/day for 9 patients for their severely active state of the disease. Plasma exchange was also performed for 2 patients. After 3 months of these treatments, activity of the disease was completely suppressed with average CRP value of 0.80 ± 2.44 mg/dl (P < 0.001 v.s. before IVIg). The elevated Cre was also significantly suppressed to 2.20 ± 1.20 mg/dl (P < 0.01) and 25 out of 30 patients showed the improvement of renal function. Significant decrease of the MPO-ANCA titers were also noted with the mean value of 41.44 ± 81.42 EU (P < 0.001). In 12 patients, ANCA were completely negative at this point. As for the overall outcome of renal function, except four patients who were started hemodialysis before treatment, no renal death was noted at 3 months, in 1 at 6 months (overall renal survival rate: 77%, and 92% except for those who were hemodialyzed before IVIg) and in another one patient after 6 months until the end of year 2003. As for the life survival, before 6 months 2 patients (survival rate 93%) and more 3 patients died after 6 months. The causes of death were cerebral bleedings for two and malignancies such as malignant lymphoma for 2 and one gastric cancer after 6 months following IVIg. It should be noted that there was no fatal infection in all IVIg treated patients.

DISCUSSION

Recently we have experienced the favorable results of IVIg monotherapy for 15 RPGN patients showing rapid decrease of CRP, WBC and ANCA titers in association with down regulation of the serum inflammatory cytokines especially of TNF α (Ito-Ihara, in submission). In the current survey, a significant anti-inflammatory effect of IVIg therapy was also proved even though the increase of the samples. In Japan survey of RPGN, 6 months renal survival rate was 70% and survival rate was 74% in MPO-ANCA positive RPGN with conventional immunosuppressant therapy (5). Comparing with these results, the 92% of renal survival rate and especially 93% life survival were remarkably high. In particular, the absence of the death due to fatal infection even following usage of the conventional immunosuppressive agents should be highly evaluated. Although more qualified evidence of beneficial effect of this therapy remains to be established in randomized controlled study, considering not only the high survival rate but the low cost for treatment of the complicated infections, the IVIg should be the potent inducible therapy which can be promoted before the beginning of conventional immunosuppressant treatment for relatively aged and lower immuno-potent MPO-ANCA patients in Japan.

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REFERENCES