Strategy of Infection Control in Immunosuppressive Therapy for ANCA-Associated Vasculitis

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Antineutrophil cytoplasmic antibodies (ANCA) are well known to be associated with small vessel vasculitic diseases such as microscopic polyangiitis (MPA), allergic granulomatous angiitis (AGA), and Granulomatosis with poly angiitis: GPA (Wegener’s). Disease assessment by 1) vasculitic activity, 2) damage resulting from vasculitis, and 3) patient function were the required endpoints for the therapeutic trials in ANCA-associated vasculitis (AAV). Harmonized steroids and cyclophosphamide or azathioprine are effective for active AAV. In evaluating tools for monitoring disease, titers of ANCA and the levels of CRP were found useful in AAV. However, it will be important for clinicians to observe AAV patients more closely and reduce immunosuppressive drug doses more cautiously, especially to prevent several infections (i.e., deep mycosis, pneumocystis jirovecii pneumonia and cytomegalovirus). We indicated that strategy of infection control in immunosuppressive therapy for AAV. (J Jpn Coll Angiol, 2009, 49: 93-99)

Keywords: compromised host, immunosuppressive therapy, ANCA associated vasculitis, infection control

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), in which antineutrophil cytoplasmic antibodies (ANCAs) are closely involved in the pathology, such as renal-limited vasculitis (RLV), Granulomatosis with poly angiitis: GPA (Wegener’s), or microscopic polyangiitis (MPA), is a systemic vasculitis syndrome mainly in the kidneys and lungs that frequently affects the older aged. In some patients, early diagnosis is made, and remission is achieved after immunosuppressive therapy with a corticosteroid (CS) and an immunosuppressant (IS) appropriate for each type and severity of disease. However, since the most frequent cause of death is infection, infection-associated factors should be analyzed, and its control measures should be established.

In this study, we evaluated the results of a nationwide epidemiological survey on AAV performed in 1988 by the Research Committee on Intractable Vasculitides, Ministry of Health, Labour and Welfare (Chairman, Hiroshi Hashimoto) and patients with complications in the prospective cohort study by the Study Group on Japanese Patients with MPO-ANCA-Associated Vasculitis (JMAAV) chairman, Shoichi Ozaki in 2008, and discussed infection occurring during immunosuppressive therapy.

Clinical Profile of AAV and its Treatment and Prognosis

Evaluation of 266 patients in the nationwide epidemiological survey on AAV in 1998 showed a male:female ratio of 1:1.7, a mean age of 56 years, a C(PR-3) AVV:(MPO) AAV ratio of 1:3, and the highest incidence of MPA, WG, or AGA (total, 121 patients), followed in order by renal-limited vasculitis (RLV) (104 patients) and vasculitis associated with collagen vascular diseases (33 patients) such as rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), and systemic sclerosis (SSc).
The clinical signs and symptoms frequently observed were systemic symptoms such as fever and weight loss, and renal [rapidly progressive glomerulonephritis: RPGN], respiratory (lung bleeding, interstitial pneumonia), and upper respiratory tract [eyes, nose, ears] manifestations. In addition, arthralgia, myalgia, skin symptoms, and neuropsychiatric manifestations were observed. The laboratory findings included an increase in ANCA correlated with disease activity, an increase in CRP, proteinuria, hematuria, azotemia/hypercreatininemia, a positive rheumatoid factor, and hyper-globumenia. The histological findings included granulomatous inflammation, capillaritis, and necrotizing angitis.1,2)

In the active stage of AAV before treatment, the ANCA titer and CRP level were high. After a decrease in the activity of vasculitis following the introduction of immunosuppressive therapy, both the ANCA titer and CRP level tended to decrease and become negative.1,2) The standard treatment method considered to be effective was combination therapy with high-dose CS and IS, mainly cyclophosphamide (CY). For RLV, plasma pheresis used in combination with the standard method was also effective for improving the outcome. Concerning the outcome of AAV, improvement/remission was observed in 60%–70% and aggravation in 10%–30%, and 41 patients died. The most frequent cause of death was infection (19 patients, 37%). The contents of infection included pneumonia and sepsis, and the most frequent causative microorganisms were fungi (such as aspergillus3)), followed in order by gram-positive bacteria (including MRSA), acid-fast bacteria, and cytomegalovirus.3)

**Table 1** Clinical findings in dead AAV cases (n = 41)

<table>
<thead>
<tr>
<th></th>
<th>I: Infection death (n = 19)</th>
<th>II: Vasculitis death (n = 22)</th>
<th>Fisher’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 y.o.</td>
<td>12/19 (63%)</td>
<td>16/22 (73%)</td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>18/19 (95%)</td>
<td>14/22 (64%)</td>
<td></td>
</tr>
<tr>
<td>RPGN</td>
<td>17/19 (89%)</td>
<td>19/22 (86%)</td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>14/19 (74%)</td>
<td>17/22 (77%)</td>
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<tr>
<td>Lung bleeding</td>
<td>3/18 (16%)</td>
<td>14/22 (64%)</td>
<td>*p &lt; 0.01</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>0/19 (0%)</td>
<td>6/22 (27%)</td>
<td>*p &lt; 0.02</td>
</tr>
<tr>
<td>CNS sym</td>
<td>1/18 (5.6%)</td>
<td>8/22 (36.4%)</td>
<td>*p &lt; 0.02</td>
</tr>
<tr>
<td>Anemia</td>
<td>4/19 (21%)</td>
<td>16/22 (73%)</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>14/19 (74%)</td>
<td>19/22 (86%)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>4/19 (21%)</td>
<td>6/22 (27%)</td>
<td></td>
</tr>
<tr>
<td>High CRP</td>
<td>19/19 (100%)</td>
<td>22/22 (100%)</td>
<td></td>
</tr>
<tr>
<td>High LDH</td>
<td>10/19 (53%)</td>
<td>16/22 (73%)</td>
<td></td>
</tr>
<tr>
<td>PSL &lt; 60 mg/day</td>
<td>8/16 (50%)</td>
<td>13/15 (87%)</td>
<td>*p &lt; 0.05</td>
</tr>
<tr>
<td>Pulse steroid therapy</td>
<td>12/17 (71%)</td>
<td>19/20 (95%)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>11/19 (58%)</td>
<td>10/22 (46%)</td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>5/18 (28%)</td>
<td>7/21 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

**Risk factors for infection in AAV patients**

Table 1 shows clinical findings in 41 patients with AAV who died, shown in 1988 by the Subcommittee on Intractable Vasculitides, Research Committee on Intractable vasculitis/epidemiology, Japanese Ministry of Health, Labour and Welfare.3) The patients were classified into Group I (19 patients who died of infection) and Group II (22 who died of vasculitis). No difference was observed in age, sex, RPGN, or renal failure between the two groups. However, the incidences of lung bleeding, gastrointestinal bleeding, and disturbed consciousness were significantly lower in Group I than in Group II (p < 0.01). The percentage of patients treated with CS (prednisolone: PSL) < 60 mg/day was significantly lower in Group I than in Group II (p < 0.05). These results suggest that continuation of the dose of prednisolone as CS ≥ 60 mg/day for AAV increases the risk of infection. Keller, et al.5) also observed long-term courses in 155 patients with WG, and reported that CY administration is indispensable for the remission of WG and prevention of its recurrence, recommending that the PSL dose should be reduced to 5–10 mg/day within 3–5 months during the remission introduction stage. As Fig. 1 shows, there were 29 cases of infection as adverse events in 19 of 50 patients in the JMAAV registry (a prospective cohort study on Japanese patients with MPO-ANCA-associated vasculitis: chief researcher, Shoichi Ozaki; chairman, Shunichi Kumagai). Of 27 patients using CY, 14 (17 cases) developed infection. Although the time of the development of infection was evaluated, various infections developed from the
including CS pulse therapy, the leukocyte (neutrophil) and platelet counts decreased to 1,200 (500)/mm$^3$ and $0.2 \times 10^4$/mm$^3$, respectively, and the patient died of respiratory failure due to pulmonary aspergillosis (confirmed by autopsy). At the time of the onset and aggravation of pulmonary aspergillosis, the anti-CSBG antibody titer acutely decreased from 1,400 to 700U. The measurement of the anti-CSBG antibody in patients with AAV is useful for evaluating the natural or acquired immune capacity of the host against β-glucan and predicting the development of deep-seated mycosis as a complication, and this antibody titer can be a clinical parameter for optimal immunosuppressive therapy for AAV and anti-infection measures. 7,8)

**Establishment of Opportunistic Infection in Patients with AAV (Immunocompromised Hosts)—Including a Draft of Anti-Infection Measures in Patients with AAV (2008)**

As shown in Fig. 4, AAV frequently develops in aged people, and induces systemic vasculitis causing disorders in the kidneys and respiratory organ as two major vital organs. As treatment, CS is administered, causing immunocompromised hosts. Fig. 3 shows a scheme of dysfunction of the immune system and the pathogen according to the type of IS. CS inhibits not only antigen processing by macrophages and antigen presentation by T cells but also interleukin 1 production and receptor expression, cellular/humoral immunity, and neutrophil function, exerting potent anti-inflammatory
Fig. 3  A 67-year-old woman with AAV Aspergillus pneumonia.9)

Fig. 4  Hypothesis of opportunistic infections in compromised AAV.
Characteristics of and Anti-Infection Measures under Immunosuppressive Therapy for ANCA-Associated Vasculitis

≥37°C fever (3 days), CRP ↑
reduce of steroids/IS
survey of infections
leukocytes (≤2000/mm³)
neutrophils, lymphocytes (≤600/mm³)
IgG ↓ (≤600 mg/dl)
serum albumin (≤3.0 g/dl)
G-CSF leukocytes <2,000/mm³
lymphocytes <500/mm³
Definite aggressive treatments
(Pneumocystis jiroveci, CMV, fungi etc)
INH 0.3g/day+Vit. B6

Fig. 5  Strategy of prevention of infections in AAV.15)

and immunosuppressive effects. On the other hand, cyclosporine inhibits interleukin 2 production and receptor expression, inhibiting cellular immunity. Azathioprine (AZ) and CY are metabolic antagonists and have myelosuppressive effects on cellular and humoral immunity, sometimes causing neutropenia.9) As shown in Fig. 3, concerning the diagnostic criteria for immunodeficiency,10) CD4 lymphocyte counts ≤200/μl indicate cellular immunodeficiency, IgG ≤600 mg/dl indicate humoral immunodeficiency, and neutrophil counts ≤600/μl indicate neutropenia. Treatment and control after the early identification of causative microorganisms using mycological, histological, and genetic tests for frequently occurring bacteria, viruses, and fungi are important. Concerning a draft for anti-infection measures in AAV (2002), we proposed the flow chart shown in Fig. 511,12) after discussion and detailed evaluation by 9 members of the Subcommittee on Treatment (Chairman, Masaharu Yoshida) of the Research Committee on Intractable Vasculitis (Chairman before the former chairman, Hiroshi Hashimoto), Ministry of Health, Labour and Welfare. AAV activity is comprehensively evaluated based on the ANCA titer, increases in the CRP and LDH levels, and characteristic signs and symptoms of vasculitis, mainly those in the lungs and kidneys.13) For AAV, optimal immunosuppressive therapy is performed with a consideration of the disease type and severity. When fever (≥37°C) persisting for 3 days or more and an increase in CRP are observed after remission of vasculitis in patients with AAV, infection as a complication is suspected. The severity of infection is evaluated based on the presence or absence of organ manifestations suggesting infection, leukocyte (neutrophil) count (<2,000 (600/mm³), lymphocyte count (CD4, 200/μl), and IgG (<600 mg/dl), and a search for and prevention of various possible microorganisms (bacteria, fungi, viruses, and protozoa) and treatment are thoroughly performed. In particular, administration of ST mixture (Baktarn®)13,14) as a treatment drug for carinii pneumonia (4–6 tablets/day/week) is useful for preventing recurrence of AAV, mainly WG, and development of carinii pneumonia as a frequent infection in AAV while gargling with Fungizone® fluid (2,400 mg Fungizone®/500 ml distilled water) and oral administration of itraconazole (ITCZ) (100–200 mg/day) are useful for preventing deep-seated fungal infection. Use of these methods in the early stage is recommended.15)

Preventive and Treatment Methods for PCP

Concerning the preventive and treatment methods for PCP, see the guidelines16) proposed by the Research Group for Complications and their Treatment Methods.
in Immunological Disease (Chief researcher, Hiroshi Hashimoto), Research Project on Allergic Disease and Immunology, Ministry of Health, Labour and Welfare.

1) Criteria for the prevention of PCP in patients with immunological diseases
   ○ Primary prevention
     *Age ≥50 years
     *Patients receiving CS
     PSL ≥1.2 mg/kg/day or PSL ≥0.8 mg/kg/day
     and concomitant use of IS
     Discontinuation criteria: PSL ≤0.4 mg/kg/day
     *Patients receiving IS
     PSL ≥0.8 mg/kg/day or peripheral leukocyte
     count ≤500/μl
     Discontinuation criteria: PSL ≤0.4 mg/kg/day,
     or peripheral lymphocyte count ≥500/μl, stably
   ○ Secondary prevention (prevention after patients
     responded once to treatment for PCP)
     *All patients who developed PCP
     Discontinuation criteria: the same as those in
     primary prevention

(2) Preventive methods for PCP
(1) ST mixture (TMP/SMX) (Baktar®: 1 tablet = 1g)
   1g/day–4 g/week (each divided dose, 2g) – 8g/week
   (each divided dose, 2g)
(2) Inhalation of pentamidine isethionate (Benanban®:
   1A = 300 mg)
   300 mg/month–300 mg/2 weeks
3) Cautionary items for examination values

Although there are differences according to age, peripheral lymphocyte counts ≤1,000/μl require attention, and preventive administration is performed. When the count is ≤500, preventive administration is recommended.

Numbers of patients with AAV who die of infection are expected to be reduced based on the flow chart in Fig. 5. PCP prevention measures under immunosuppression for AAV, and early treatment.

CONCLUSION

We outlined mainly the characteristics of and measures against infections as complications associated with immunosuppressive therapy for vasculitis, and described the results of analysis of AAV as intractable vasculitis that requires potent immunosuppressive therapy and causes many deaths due to infection.

ACKNOWLEDGMENTS

We express deep gratitude to the members and Prof. Hiroshi Hashimoto (Chairmen before the former chairman) of the Subcommittee on Treatment for ANCA-Associated Vasculitis-Research Committee on Intractable Vasculitis, Ministry of Health, Labour and Welfare, JMAAV Committee (Chairman, Shoichi Ozaki), JMAAV Complication Evaluation Committee (Chairman, Kumagai Shunichi), and the Research Committee on Complications and Treatment Methods for Immunological Diseases (Chief researcher, Hiroshi Hashimoto) for their cooperation.

DISCLOSURE STATEMENT

None.

REFERENCES

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