Novel Strategy for the Treatment of Refractory Vasculitis Syndrome

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The recent development of biologic therapies capable of selectively targeting components of the immune system has revolutionized the treatment of inflammatory arthritides. The increase in the use of biologic agents coupled with expansion in the knowledge of the pathogenesis of vascular inflammation has led to their application in the treatment of primary systemic vasculitis. Biological therapies appear to have a place in the therapeutic strategy for ANCA-associated systemic vasculitides, at least for patients whose disease is refractory to conventional therapy. The use of biologics as targeted therapies has also, in reverse, improved our understanding of the pathophysiology of vascular inflammation. However, the precise indications for TNF-alpha inhibitors or anti-CD20 monoclonal antibodies have not yet been defined. These biologics must be prescribed extremely cautiously and only in trial settings, especially in view of the adverse effects. (*English Translation of J Jpn Coll Angiol, 2009, 49: 75-79)

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INTRODUCTION

Primary vasculitis syndrome includes a wide variety of diseases from great-vessel to small-vessel vasculitis, all of which are refractory chronic diseases. Regarding Wegener’s granulomatosis, which is a typical primary vasculitis, the 5-year survival rate was reported to be 53% in the era when it was treated with steroid alone, but the mortality rate decreased to 12% in 8 years after the introduction of the cyclophosphamide-steroid combination therapy by the NIH, USA. However, severe complications due to side effects posed a major problem. Efforts to reduce drug-related complications have been made since 1990, and measures including rapid decreases in the dose of steroid, shortening of the period of cyclophosphamide administration, and its replacement with a less toxic immunosuppressant have been evaluated primarily in Europe, resulting in the establishment of many treatments to improve the prognosis. However, drug-related complications and reactivation of the disease still remain important problems, and the development of more effective and safer treatments is needed.

In this article, the latest information primarily about TNF-α inhibitors and anti-B cell antibodies, which are biologics attracting attention as possible treatments for vasculitis, is presented.

USEFULNESS OF ETANERCEPT FOR THE TREATMENT OF WEGENER’S GRANULOMATOSIS

To evaluate the usefulness of etanercept, a multi-center collaborative double-blind randomized placebo controlled study was carried out by an American expert group. First, patients with active Wegener’s granulomatosis were divided into 2 groups and a standard treatment protocol was performed in for each group. A recent development that study was that the patients with systemic or localized Wegener’s granulomatosis were classified according to the severity, i.e., whether there is...
the risk of death or insufficiency of important organs, rather than by the conventional scale of whether there were renal lesions. Thereafter, as a standard protocol for remission induction, 2 mg/kg/day cyclophosphamide plus 0.5–1 mg/kg/day prednisolone was prescribed for systemic Wegener’s granulomatosis and 25 mg/week methotrexate (MTX) (gradually increased from 0.25 mg/kg/week) plus steroid for localized Wegener’s granulomatosis. In both groups, the steroid administration was gradually reduced and discontinued after 6 months. Once remission was induced after 3–6 months, MTX was administered to both groups for 12 months as a remission maintenance therapy and was gradually discontinued after 6 months. Once remission was induced after 3–6 months, MTX was administered to both groups for 12 months as a remission maintenance therapy and was gradually discontinued. Patients in whom the serum creatinine level was 2.0 mg/dl or higher were administered azathioprine at 2 mg/kg/day instead of MTX. Thus, the registered patients were stratified according to the severity, those in each stratum were divided at random into 2 groups and followed up for at least 12 months while administering 25 mg etanercept or placebo 2 times/week. When the keys were opened after the end of the study, etanercept and placebo were administered to 89 and 91 patients, respectively, and no significant difference was noted in the remission induction rate, reactivation rate after remission, or dropout rate. However, severe adverse effects were observed in many patients of both groups, i.e., 56% in the etanercept group and 57% in the placebo group. Infections were observed in 49% of both groups, and deep venous thrombosis was noted in 10 patients in each group. The most important adverse effect was the occurrence of solid cancer observed in 6 patients, all belonging to the cyclophosphamide+etanercept group. The incidence of solid cancer has been reported to be 2–6 times higher in patients with Wegener’s granulomatosis compared with gender- and age-matched general population, and the cyclophosphamide administration has been known to increase in the incidences of bladder cancer and hematologic malignancies. However, the 6 patients consisted of 2 with mucous adenocarcinoma and 1 each with bile duct cancer, kidney cancer, breast cancer, and liposarcoma, which differed from cyclophosphamide-related tumors. Also, no difference was observed between the two groups in gender, smoking history, drinking history, clinical or familial history of malignant neoplasms, or the dose of cyclophosphamide during the study or in the past except that the age was higher in the etanercept group than in the control group. Therefore, the occurrence of solid tumors was judged to have been induced by the addition of etanercept to the standard immunosuppressive therapy. In conclusion, the concomitant use of etanercept for the treatment of Wegener’s granulomatosis should be avoided, because it is not only ineffective for the induction of remission or prevention of reactivation but is also likely to resulting the occurrence of solid cancers.

**Usefulness of Infliximab for the Treatment of ANCA-Associated Vasculitis**

Compared with etanercept, infliximab not only has stronger binding with TNF-α but also has a different action mechanism: Three molecules of infliximab can bind to 1 molecule of TNF-α and, in binding with membrane binding TNF, it activates complement and lyses cells expressing TNF-α. Whether such differences reflect differences in the clinical effect is unclear, but they may be related to the differences in the efficacy of the two drugs against Crohn’s disease, and Behçet’s disease. Therefore, infliximab may be expected to have effects different from those of etanercept against Wegener’s granulomatosis, a granulomatous inflammatory disease. There has been no comparative study evaluating the usefulness of infliximab against Wegener’s granulomatosis. However, 4 open pilot studies have been reported along with case reports suggestive of its usefulness. Of the 54 cases included in the 4 reports, 35 had Wegener’s granulomatosis, and 16 had microscopic polyangiitis. Thirty-seven of the 54 cases were refractory cases in which remission could not be induced by a standard immunosuppressive therapy. In addition to conventional immunosuppressants, infliximab was administered at 3–5 mg/kg at intervals of 4–8 weeks, resulting in induction of remission in 43 (81%). Booth, et al., reviewing 32 cases, reported that remission could be achieved very early, i.e., a mean of 6.4 weeks after the introduction of infliximab. In the 33 cases followed up for 1 year or longer, remission could be maintained for 6 months or longer in 28 (85%), and reactivation after remission was observed in 5 (12%). Concerning the safety, 6 contracted infections, 2 were suspected to have infections, and 2 died. The deaths were due to refractory alveolar hemorrhage and bronchial pneumonia. No adverse event related to malignant neoplasm was reported. These results of open pilot studies suggest relatively short-term usefulness of infliximab against ANCA-associated vasculitis.

However, in a recent prospective study, infliximab was administered at 5 mg/kg 5 times in a 6-month period
to 9 patients with various vasculitides including 3 with Wegener’s granulomatosis, but no significant improvement in the BVAS score was noted, and the study was discontinued due to the appearance of serious adverse events such as the induction of lupus-like syndrome accompanied by anti-nuclear antibody and anti-DNA antibody and vasculitis in 4 patients, exacerbation of the disease in 6, and death due to heart failure in 1. Since etanercept has also been reported to possibly induce solid cancers, no comparative study to validate the usefulness of infliximab is underway.

**USEFULNESS OF RITUXIMAB FOR THE TREATMENT OF ANCA-ASSOCIATED VASCULITIS**

In 11 patients with Wegener’s granulomatosis (complicated by active lung lesions in 7) in whom remission could not be induced by a standard therapy, the conventional immunosuppressive therapy was discontinued, and rituximab and prednisolone at 1 mg/kg or less were administered. Rituximab was administered by intravenous drip infusion by repeating a course of 375 mg/m² 4 times at 1-week intervals. As a result, remission could be induced in all patients within 6 months, and no reactivation was noted during the period in which peripheral blood B cells were absent. Of the 9 patients in whom B cells re-appeared within 1 year after a course of treatment, an elevation of ANCA and reactivation of vasculitis were noted in 2, but they were remitted by the re-administration. This group further performed the same treatment in 10 patients with ANCA-associated vasculitis and reported similar effects. Another group also reported similar efficacy of rituximab by a long-term follow-up of 2–4 years.

Rituximab is considered promising as a new treatment for ANCA-associated vasculitis, and its multi-center collaborative prospective clinical studies are being conducted in Europe and the US. At our department, also, a pilot study using rituximab was carried out in 3 patients with Wegener’s granulomatosis, and remission could be achieved in all patients including 1 patient having granulomatous lesions in the lung.

**TNF-α INHIBITORS AGAINST TAKAYASU DISEASE**

Remission cannot be maintained over a long period with steroid alone in about half the patients with Takayasu disease. In such patients MTX and azathioprine were administered in combination. In 2004, the results of a pilot study to evaluate the usefulness of TNF-α inhibitors in 15 patients in whom the dose of steroid was difficult to reduce to maintain remission or reactivation was observed during the treatment with immunosuppressants were reported. It was difficult to reduce the dose of steroid even by the concomitant use of immunosuppressants such as MTX in 13. Etanercept was administered at 25 mg 2 times a week in 7, and infliximab was administered at 3–5 mg/kg (intravenous drip infusion in Weeks 0, 2, 6, and every 4–8 weeks thereafter) in 8. Alleviation of inflammation was noted in 14. In 10, remission was maintained for 1–3.3 years after weaning from steroid, and no new vascular lesion was noted. In 15 patients, the median maintenance dose of steroid was 20 mg (12.5–40 mg/day) before the beginning of TNF-α inhibitor therapy but could be reduced to 0 mg (0–20 mg/day) after its beginning, and 10 could be weaned from steroid. Of the 14 patients who showed improvements, 7 required increases in the dose of the TNF-α inhibitor or a change of the drug. Etanercept was increased from 25 mg 2 times/week to 50 mg 2 times/week in 2 of the 4 patients, and it was substituted for infliximab, resulting in remission. Of the patients administered infliximab, its dose was increased to 7 mg/kg in 3, resulting in remission. As adverse events, disseminated histoplasmosis and herpes zoster were observed in 1 patient each, but they could be controlled by treatment. Thereafter, case reports suggesting the usefulness of infliximab for the treatment of refractory Takayasu disease have appeared from various countries including Japan. Evaluation by large-scale comparative controlled studies is necessary in the future.

On the other hand, tocilizumab, an anti-IL-6 receptor antibody preparation developed in Japan, has been demonstrated to be effective for the treatment of Castleman’s disease and rheumatoid arthritis and is used clinically, and cases suggestive of its usefulness for the treatment of refractory Takayasu disease have also been reported from Osaka University. Future clinical trials are needed.

**GIANT CELL ARTERITIS**

This disease, which occurs frequently in elderly people, has been reported to remit in many patients by steroid therapy and not to affect the quality of life. The greatest complication is loss of vision due to ophthalmic artery lesions, but it occurs before the beginning of
steroid therapy in most patients, and only about 1% of the patients develop it after steroid therapy has been initiated. If other immunosuppressants are necessary in patients with such a disease, the objective of their use is to reduce the side effects of steroid such as osteoporosis by reducing its dose. Since this disease is characterized by granulomatous inflammation, and since a large amount of TNF-α is detected at the lesion, anti-TNF-α antibody was expected to be useful for its treatment. In an RCT performed in the US, the subjects were divided at random at a ratio of 2:1 for 5 mg/kg infliximab and placebo, respectively, after induction of remission with prednisolone, and intravenous drip infusion was carried out in Weeks 0, 2, and 6 and every 8 weeks thereafter. The reactivation rate during 22 weeks was 43 and 50%, respectively, and the dose of prednisolone could be reduced to 10 mg or less in 61 and 75%, respectively, showing no significant difference. As a result, 28 and 16 patients were registered as infliximab and placebo groups, respectively, and the clinical trial was discontinued after the observation period was shortened from initially intended 54 weeks to 22 weeks. Eventually, no difference was observed in the remission maintenance rate, total dose of steroid, or side effects. These results showed that infliximab has no marked effects at least as a remission maintaining drug. Various lessons can be derived from this clinical trial, which ended in failure. First, there was a problem with the study design. Since giant cell arteritis is a disease that is intrinsically responsive to steroid therapy, the percentage of patients in whom infliximab plays an important role is expected to be low. The subjects should have been restricted to those who responded insufficiently to steroid. Secondly, the protocol of this study required to reduce the steroid dose earlier than usual. The administration of prednisolone was initiated at 40–60 mg/day, the dose was reduced after Week 2 to 20 mg/day at a rate of 10 mg/week, then to 10 mg/day at a rate of 2.5 mg/2 weeks, and continued to be reduced thereafter until the administration was discontinued by Week 22. This study was beneficial in that it demonstrated that steroid can be reduced by such a rapid pace to discontinuation by Week 22 without reactivation in 50% of the patients (placebo group). Thirdly, TNF-α was found not to play an important role in the prolongation of the activity or reactivation of giant cell arteritis. The roles of dendritic cells and cytokines such as IL-6 may be more important. Clinical trials using drugs such as tocilizumab (anti-IL-6 receptor antibody) are needed.

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