OBSERVATION

Long-term B-Lymphocyte Depletion With Rituximab in Patients With Relapsing-Remitting Multiple Sclerosis

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Objective: To describe 2 patients with relapsing-remitting multiple sclerosis (RRMS) receiving long-term treatment with the monoclonal antibody rituximab. The clinical and paraclinical efficacy of rituximab was demonstrated recently in a phase 2 clinical trial in patients with RRMS.

Design: Case series.

Setting: Tertiary care university medical center.

Patients: Two young patients with highly active RRMS in whom standard therapy had failed before receiving rituximab for up to 48 months.

Main Outcome Measures: Relapse rate, clinical disability, and results of magnetic resonance imaging.

Results: Both patients tolerated rituximab treatment well and have been clinically stable throughout the study period.

Conclusion: Long-term therapy with rituximab appears safe and effective in some patients with RRMS. Our observation should be confirmed in controlled long-term trials.

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Substantial evidence suggests that B-lymphocyte responses against unidentified antigens contribute to the immunopathogenesis of multiple sclerosis (MS), an inflammatory autoimmune disorder of the central nervous system.[1,2] Rituximab (Roche Pharma, Reinach, Switzerland) is a genetically engineered chimeric IgG1 κ monoclonal antibody targeting the B-lymphocyte surface antigen CD20. Treatment with rituximab results in a decrease of circulating B lymphocytes.

Two recently published clinical trials provide evidence of treatment efficacy of rituximab in patients with relapsing-remitting MS (RRMS). The first study was a phase 2, double-blind 48-week trial in which patients received 2000 mg of rituximab intravenously within 2 weeks.[3] The second study was a 72-week, open-label phase 1 trial in which patients received 2 courses of rituximab therapy 6 months apart for a total dose of 4000 mg.[4] However, the duration of the treatment effect and the safety and efficacy of long-term rituximab therapy beyond 72 weeks have not yet been addressed.[5]

REPORT OF CASES

PATIENT 1

We previously described a patient with RRMS treated with rituximab,[6] who at the time of treatment initiation was 27 years of age. In this patient, complete depletion of B lymphocytes in the peripheral blood and cerebrospinal fluid of $CD20^+$ B cells, assessed by flow cytometry was detectable 9 months after the last of 3 rituximab infusions. The recurrence of B lymphocytes was associated with the appearance of new gadolinium-enhancing lesions on magnetic resonance imaging but not with clinical disease activity. Consequently, the patient underwent additional treatment with 2 intravenous 1000-mg doses of rituximab 2 weeks apart at 6- to 9-month intervals. Since initiation of rituximab therapy, he has received 6 courses of rituximab treatment for a cumulative dose of 13 000 mg within 204 weeks. The patient initially continued to improve clinically and with regard to surrogate disease markers on magnetic resonance images. He has had no disease relapse within the past 48 months, in

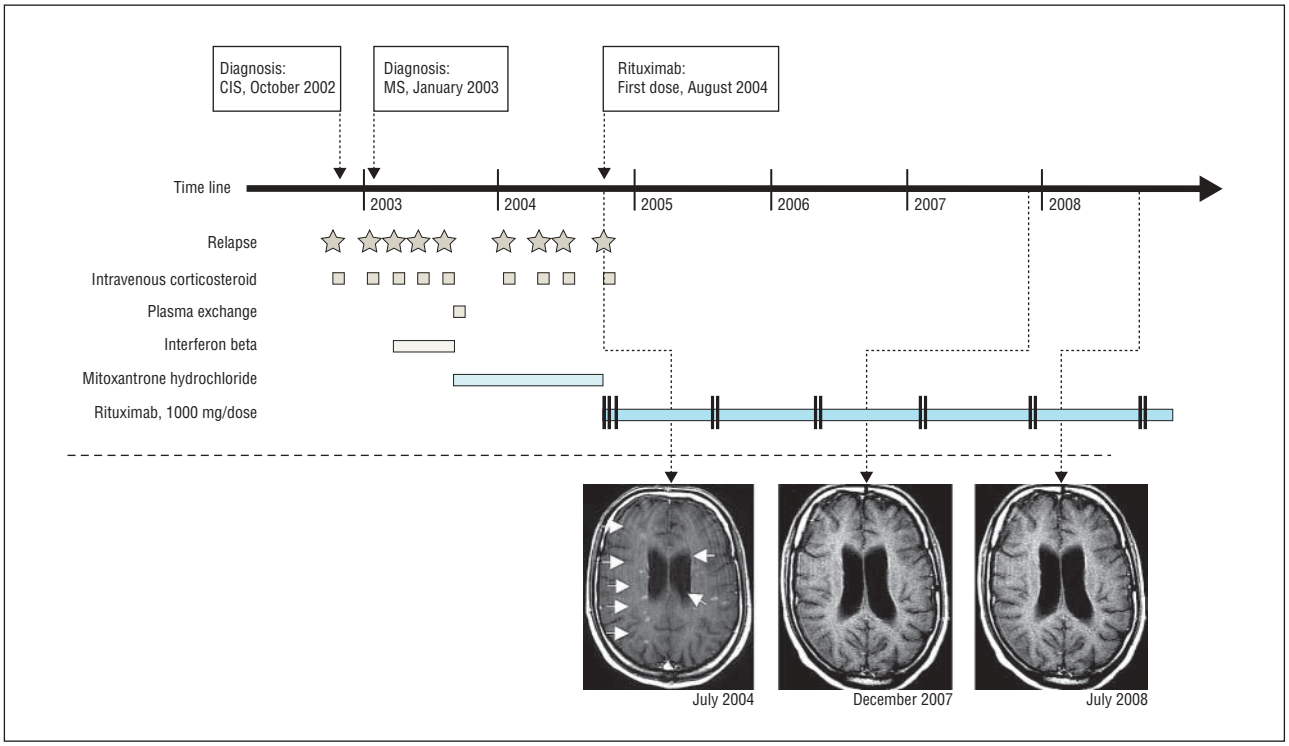

Figure. Therapeutic regimens and the clinical and paraclinical course of patient 1 after treatment with the monoclonal antibody rituximab. CIS indicates clinically isolated syndrome; MS, multiple sclerosis. The magnetic resonance images (T1 weighted, after application of gadolinium) reveal blood-brain barrier damage before rituximab therapy, as seen by contrast-enhancing lesions (arrows), whereas during therapy no evidence of acute inflammation could be observed.

contrast to the 23 months before rituximab therapy, when he experienced 9 relapses. He did not require any further pulsed corticosteroid treatment. His Expanded Disability Status Scale score was 6.0 before receiving rituximab therapy. The score improved to 4.0 in the first 9 months and gradually improved to 3.0 for the past 30 months (**Figure**). All 13 infusions have been tolerated without any adverse effects, and we have not noticed any adverse events thus far.

PATIENT 2

The second patient is a 23-year-old white man with very active RRMS that failed to respond to any of the approved first-line therapies. Therefore, rituximab therapy was initiated 160 weeks ago at the same dose and frequency as for patient 1. Ten months after the first treatment course, he experienced another relapse. At that time the B-lymphocyte count had returned to baseline values in the peripheral venous blood as well as in the cerebrospinal fluid. Treatment with rituximab was continued at 6- to 9-month intervals. The patient has since been relapse free and stable clinically and with regard to paraclinical measures. He has received 9 infusions for a total dose of 9000 mg of rituximab, which he has tolerated well.

COMMENT

These 2 cases demonstrate that a complete depletion of B lymphocytes through targeting of the CD20 molecule can significantly reduce relapse rate and progression of clinical disability in patients with RRMS. The recurrence of paraclinical disease activity 9 months after the first course of rituximab therapy in association with the recurrence of B lymphocytes in the peripheral venous blood and in the cerebrospinal fluid in patient 1 and a clinical relapse 10 months after the first course of the antibody treatment in patient 2 suggest that the recurrence of B lymphocytes is associated with reactivation of inflammatory disease activity. We do not fully understand how B-lymphocyte depletion translates into the apparent rapid and sustained clinical efficacy in our 2 patients. The persistence of circulating antibodies and the observation that rituximab reduces the number of T cells in the cerebrospinal fluid[7] argue that rituximab exhibits its effects via mechanisms other than the inhibition of B-lymphocyte differentiation into antibody-secreting plasma cells. Depletion of B lymphocytes may affect the elaborate cytokine network between different leukocyte populations. In addition, it is likely that the monoclonal antibody treatment impairs the antigen-presenting function of B cells. Overall, these findings emphasize the relevant role of B lymphocytes in the immunopathogenesis of MS, at least in a subset of patients.

The recurrence of B lymphocytes in patients treated with rituximab can vary between individuals. Thus, the treatment intervals we used were based on initial B-lymphocyte assessments in the individual patient. Repeated treatment with rituximab at 6- to 9-month intervals was safe and well-tolerated in both of our patients for an observational period of up to 204 weeks. However, opportunistic infections, including progressive multifocal leukoencephalopathy, have been

reported with rituximab.[8,9] Hence, pharmacovigilance is clearly required when treating patients with this antibody.

These encouraging clinical observations in 2 patients should be confirmed in controlled long-term trials.

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