Novel Use of Dual Immunomodulation for Treating Stiff-Person Syndrome, Cerebellar Variant

Stiff-person syndrome is an autoimmune syndrome defined by muscle spasms and rigidity of proximal and axial muscles. Glutamic acid decarboxylase is the autoantigen found in 60%–80% of stiff person syndrome patients.[1,2] Stiff person syndrome, cerebellar variant was characterized in a subpopulation of patients (5 of 38) with stiff person syndrome and concomitant cerebellar dysfunction[3] and confirmed in another case series (3 of 61).[4] In both case series, increased intrathecal synthesis of anti–glutamic acid decarboxylase antibodies was found in stiff person syndrome, cerebellar variant patients. Gamma-aminobutyric acid agonists such as diazepam and immunotherapies improved their stiffness but not cerebellar dysfunction.[3] In this case report we evaluate a therapy using rituximab and cyclophosphamide; this dual immunomodulation improved both stiffness and cerebellar function in our patient.

Patient and Methods

The patient was given 6 weeks of weekly rituximab (375 mg/m^2) and cyclophosphamide biweekly (800 mg/m^2), followed by monthly cyclophosphamide (800 mg/m^2), for a total of 12 cycles. After her 12th cycle of cyclophosphamide, she was given a drug holiday. She resumed therapy 5 months later with rituximab, weekly for 4 weeks (375 mg/m^2), combined with 1 week of cyclophosphamide (800 mg/m^2) and followed by monthly cyclophosphamide (800 mg/m^2). She is currently managed with maintenance rituximab (375 mg/m^2) every 6 months, weekly for 4 weeks, combined with 1 dose of cyclophosphamide (800 mg/m^2) and between combination treatments, with monthly cyclophosphamide (800 mg/m^2). Response was measured with the Scale for Assessment and Rating of Ataxia[5] and anti–glutamic acid decarboxylase titers (Fig. 1a,b). Leukocyte counts and cluster of differentiation 4 subsets were also monitored.

Results

She was placed on therapy with 4 weeks of weekly rituximab (375 mg/m^2) and cyclophosphamide biweekly (800 mg/m^2) followed by 8 cycles of monthly cyclophosphamide (800 mg/m^2). Four months later deterioration occurred; Rituximab and cyclophosphamide were resumed. Therapeutic response was measured clinically with the Scale for Assessment and Rating of Ataxia and anti–glutamic acid decarboxylase titers, and during these treatments, both these parameters improved, which correlated with clinical improvement. Leukocytes and cluster of differentiation 4 counts were monitored, and the therapies were stopped temporarily if there was evidence of leukocytosis. She was maintained on this regimen because she improved clinically.

Discussion

Ishida et al isolated cerebrospinal fluid anti–glutamic acid decarboxylase immunoglobulin G antibodies from a stiff person syndrome, cerebellar variant patient and demonstrated suppression of gamma-aminobutyric acid–mediated transmission from cerebellar basket cells but not cerebellar Purkinje cells, which may explain why ataxia is characteristic of stiff person syndrome, cerebellar variant.[6] Rituximab has been used previously in the successful treatment of stiff person syndrome.[7] Cyclophosphamide monotherapy does not work in stiff person syndrome. Because rituximab targets B cells and cyclophosphamide, among its multiple mode of actions, also targets T cells, dual immunomodulation was chosen. ■

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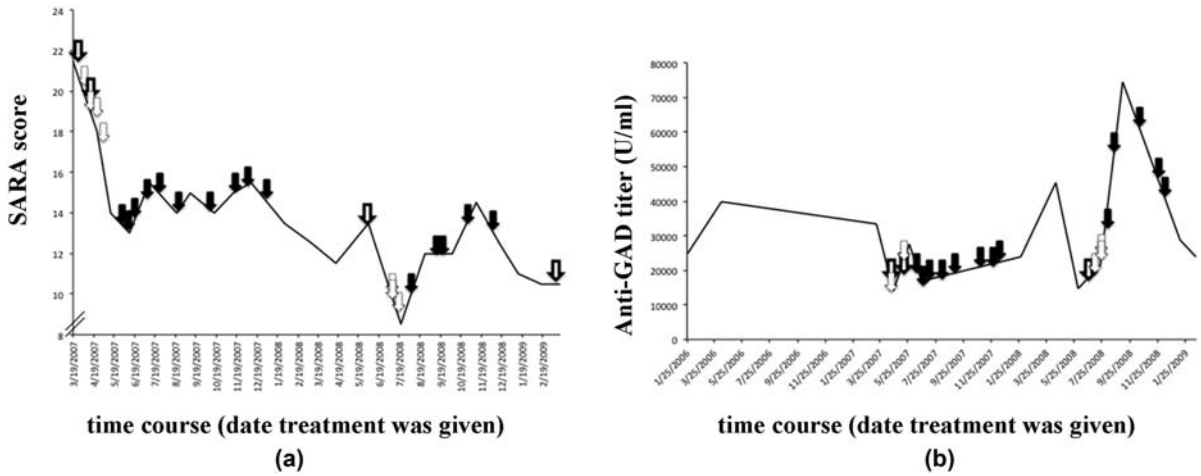

FIG. 1. a: Treatment time course versus Scale for Assessment and Rating of Ataxia score. The black arrow is cyclophosphamide + rituximab (CPA + rituximab), the black outlined arrow is cyclophosphamide (CPA) monotherapy, and the dashed arrow is rituximab monotherapy. **b:** Treatment time course versus anti–glutamic acid decarboxylase antibody titer. The black arrow is CPA + rituximab, the black outlined arrow is CPA monotherapy, and the dashed arrow is rituximab monotherapy.

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