Recombinant Human Soluble Thrombomodulin for Treatment of Thrombotic Microangiopathy Associated with Lupus Nephritis

To the Editor:

Thrombotic microangiopathy (TMA) is a rare but frequently life-threatening complication of systemic lupus erythematosus (SLE). TMA is associated with a worse overall prognosis and usually requires plasma exchange in addition to immunosuppressive therapy. We treated a 33-year-old woman with SLE who developed TMA and renal dysfunction; she was diagnosed with nephrotic syndrome due to complicated severe lupus nephritis (LN). From the hypertension, headache, thrombocytopenia, and elevated D-dimer, malignant hypertension with possible TMA was considered.

She was immediately treated with methylprednisolone 1 g pulse therapy for 3 consecutive days, followed by prednisolone 60 mg/day. In addition, she received nifedipine and telmisartan to treat hypertension. Despite improvement of hypertension, her serum creatinine level was further elevated to 1.05 mg/dl and thrombocytopenia progressed to 40,000/µl within 4 days after admission. Moreover, plasma fibrinogen level decreased to 166 mg/dl. Although we speculated that her condition was either lupus-associated TMA or disseminated intravascular coagulation (DIC), a definitive diagnosis of TMA was suspended at this point because we failed to detect red cell fragmentation in the blood smears. Therefore, we started daily IV infusion of rTM 380 U/kg/day on Day 4. Just after the start of rTM, her serum creatinine level improved.

As treatment for LN, IV cyclophosphamide (CYC) was administered at 500 mg/day (0.9 mg/kg body weight) on Day 8. Detection of fragmented red cells on her blood smear on the following day led us to diagnose TMA associated with LN. Because of the negative Coombs test and normal prothrombin time and activated partial thromboplastin time, we excluded autoimmune hemolytic anemia and DIC. During the rTM therapy, we observed improvement of her serum creatinine, lactate dehydrogenase, fibrin degradation products, and platelet counts. Finally, on Day 18, when the disappearance of fragmented red cells was noted, the rTM infusion was discontinued. No adverse effects were noted. The prednisolone dosage was gradually tapered, and IV CYC was repeated intermittently. The proteinuria disappeared and serum creatinine level normalized. She was discharged on Day 56, and has remained in remission for more than 10 months.

The pathogenesis of TMA with SLE has not been fully elucidated. Possible explanations include malignant hypertension, antiphospholipid syndrome, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, diffuse small-vessel vasculitis, and nephritis. One hypothesis is that autoantibodies may result in a decrease in ADAMTS13, although some TMA patients with SLE showed normal ADAMTS13 activity. In our case, serum ADAMTS13 was 69.8%, almost within the normal range (reference range 70%~120%).

Current therapy for TMA with LN consists of a combination of immunosuppressive therapy and plasma exchange; there are doubts about the safety of this treatment. Since 2008, rTM has been introduced for the treatment of DIC in Japan, based on a clinical trial. rTM comprises the active extracellular domain of thrombomodulin, and inactivates coagulation by binding to thrombin. In addition, thrombin-rTM complexes activate protein C. The resultant activated protein C inactivates factors VIIIa and V, inhibiting further thrombin formation. Additionally, rTM has been shown to exert antimflammatory activity by binding to and inactivating high-mobility group box 1 (HMGB1) protein. By this mechanism, rTM has been shown to inhibit endothelial injury and to protect against ischemic damage in the kidney.

These antimflammatory and anticoagulant effects of rTM may have contributed to the improvement of TMA with LN in our case. rTM appeared to have a therapeutic potential with fewer adverse effects compared with plasma exchange and to be useful for SLE-associated TMA. Further studies are required to confirm this.

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