中文題目：Mycophenolic acid 治療紅斑性狼瘡病人難治的自體免疫溶血性貧血

英文題目：Successful treatment of refractory autoimmune hemolytic anemia with mycophenolic acid in a systemic lupus erythematosus patient

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Introduction:

Autoimmune hemolytic anemia (AIHA) has been reported in up to 10% of patients with systemic lupus erythematosus (SLE). Glucocorticoids are used as first-line therapy in these patients, but there is no conclusive evidence to guide second-line therapy. Herein we present a case of SLE with severe AIHA and thrombocytopenia who was refractory to glucocorticoid treatment, splenectomy and successfully treated by mycophenolic acid.

Case Presentation:

A 45 -year-old female diagnosed as SLE with initial characteristics of anemia, thrombocytopenia, and fever, at the age of 18. She had received methylprednisolone (MTP) pulse therapy and Intravenous immunoglobulin (IVIG) for several times due to refractory anemia and thrombocytopenia. Then she received prednisolone and hydroxychloroquine for long term treatment. Since 2005, she had hospitalization several time for hemolytic anemia with positive direct Coombs' test, elevated LDH and bilirubin, and splenomegaly was found. Azathioprine was added to combine prednisolone and hydroxychloroquine. She still had several episodes of severe AIHA each year, and thus she received high dose methylprednisolone therapy, IVIG, as well as rituximab on 2009/9/29, 2010/5/18, 2011/1/16, 2011/4/19 and 2012/6/25. However, in 2012/10, worsening anemia (hemoglobin, Hb: 4.4 g/dl), thrombocytopenia (platelet 56,000 /uL), low level of C3/C4 (34.2/3.28 mg/dL), and proteinuria (UP/CR: 2.87g/day) were found and she received splenectomy on 2012/10/05. Unfortunately, she experienced abdominal pain on 2012/10/23 and thrombosis of superior mesenteric vein, splenic vein and main portal trunk (negative for antiphospholipid antibodies) was found. Warfarin was prescribed. However, she suffered from ischemic stroke in right middle cerebral artery territory in 2013/3. In following years, she was under treatment with prednisolone and azathioprine daily but still had frequent admission (4-5 times/year) for symptomatic AIHA. Her AIHA was resolved by receiving methylprednisolone pulse therapy.

In 2017/04, for refractory AIHA, Hb:8.5g/dl, mycophenolic acid (MPA, total 720mg per day) was added. She had Hb:10-11g/dl in following months but had decrease to 7.5g/dl in 2017/10. Thus, mycophenolic acid was titrated up from 1080mg per day (2017/12) to 2160mg per day (2018/11), during which her Hb around 10-14 g/dl and platelet count was maintained above lower limit of normal range, with steady dose of mycophenolic acid 2160mg per day, From2020/06 to 2022/07, her Hb was in the 8.7-14.1mg/dl range and remained transfusion independent.

Discussion:

Patients with SLE may present with AIHA and thrombocytopenia concomitantly or sequentially, known as Evans syndrome. Evans syndrome associated with SLE is rare and often precedes the onset of SLE. Most patients respond adequately to high-dose steroids (prednisolone 1mg/kg) with gradual dose tapering. In 10% of patients, AIHA is refractory or relapsing necessitating a second-line treatment. Physicians may

consider immunosuppressants, such as azathioprine, cyclosporine, intravenous immunoglobulin, cyclosporine, mycophenolate mofetil, danazol, bortezomib, anti-CD20 monoclonal antibody (rituximab, ofatumumab), or splenectomy.

This patient was refractory to steroid and multiple second-line agents of treatment. Although, her thrombocytopenia had partial response to splenectomy. She still had recurrent severe AIHA and required frequent admission to receive pulse therapy and transfusion. MPA is a potent, selective, noncompetitive inhibitor of the type 2 isoform of inosine monophosphate dehydrogenase (IMPDH) expressed in activated T and B lymphocytes. By inhibiting IMPDH, MPA depletes the pool of dGTP required for DNA synthesis and has a more potent cytostatic effect, specifically blocks the proliferation of B and T lymphocytes. In combination of low dose of steroid, MPA has a useful role as a second-line agent to treat this SLE patient with AIHA and autoimmune thrombocytopenia. The effect was dose-dependent.

Conclusion:

Despite many treatment options, many SLE patient with AIHA are refractory to glucocorticoid treatment. In our experience, a combination of a selective inhibitor of purine synthesis, mycophenolic acid, may be an alternative therapy.