Successful treatment with belimumab in a patient with refractory systemic lupus erythematosus after initiation of hemodialysis: Considering the synergistic effect of belimumab and immunological burn-out phenomenon in end stage renal disease patients on hemodialysis

**CURRENT STATUS:** POSTED

Shota Ogura  
Tokyo Women's Medical University

Kazunori Karasawa  
Tokyo Women's Medical University

ichitoku@hotmail.co.jp**Corresponding Author**

Wataru Ono  
Tokyo Women's Medical University

Ayaki Ito  
Tokyo Women's Medical University

Momoko Seki  
Tokyo Women's Medical University

Yoshiko Yamaguchi  
Tokyo Women's Medical University

Miwa Kamizawa  
Tokyo Women's Medical University

Mai Tosaka  
Tokyo Women's Medical University

Yusuke Ushio  
Tokyo Women's Medical University

Naoko Sugiura
Abstract

Background: In patients with systemic lupus erythematosus (SLE), disease activity can persist even after initiating dialysis. However, guidelines for the treatment of patients with SLE after dialysis is initiated have not yet been established.

Case presentation: We describe the case of a 62-year-old Japanese woman who was diagnosed with SLE at age 12, progressed to end-stage renal disease (ESRD), and initiated hemodialysis for lupus nephritis. However, SLE activity persisted after hemodialysis. Cyclophosphamide and mycophenolate mofetil were administered in addition to prednisolone and immunoadsorption, but this treatment strategy was limited by side effects. The patient was subsequently treated with belimumab, and the activity of SLE decreased rapidly.

Conclusions: ESRD patients with SLE show no significant decrease in transitional B cells, and have elevated levels of B-cell activating factor (BAFF). Both transitional B cells and BAFF are important therapeutic targets for belimumab, indicating that patients with ESRD may benefit from belimumab therapy. However, the effects of belimumab may be potentiated in patients with uremia, who may be more susceptible to adverse events such as infections. Patients with SLE who receive belimumab after initiation of hemodialysis therefore require careful follow-up. Here we report the first case of belimumab administration in a patient with SLE after initiation of hemodialysis.

Background

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease caused by autoantibodies and tissue deposition of immune complexes. The main etiology of SLE is a loss of immunological tolerance for auto-antigens, with progression to a chronic inflammatory condition. [1] The treatment of SLE has evolved around the suppression of various immune responses in the process leading to chronic inflammation. To date, the treatment of SLE according to the degree of severity has been recommended in international guidelines. [2][3] However, there are no guidelines for the treatment of patients with SLE after initiation of dialysis, partly because it remains unclear how the immune response in these patients differs from that in patients with healthy kidneys. Furthermore, the incidence of side effects is high in these patients because the pharmacokinetics of
the drug used for treatment differ from those observed in non-dialysis patients. Regardless of whether a patient is on dialysis, SLE is thought to involve the activation of B cells, and the production of autoimmune antibody at disease initiation has resulted in the establishment of SLE as a B-cell-driven disease. [4] Compared with other immunosuppressants that affect renal metabolism, biological agents can be used relatively safely, regardless of renal status. [5] Given this background, belimumab has been shown in recent years to be effective in the treatment of SLE. [6] Belimumab is a complete human type IgG1 lambda antibody that binds to B-cell activating factor (BAFF) receptor on B cells to inhibit soluble BAFF or B-cell survival and function. Patients with SLE show excess secretion of BAFF, which may result in inappropriate survival of autoreactive B cells. [7] However, there have been no reports to date of the use of belimumab as treatment for SLE in patients who have initiated dialysis. In the case reported here, lupus nephritis resulted in end-stage renal disease (ESRD) and hemodialysis was initiated. The patient had a 42-year history of SLE treatment with various regimens such as steroids, cyclophosphamide, mycophenolate mofetil, and immunoadsorption, but remained in a prolonged serologically active state with a high possibility of major flare up. Here we report the first case of belimumab administration in a patient with SLE after initiation of hemodialysis.

Case Presentation

A 54-year-old woman was diagnosed with SLE and lupus nephritis 42 years previously. She had no family history.

At diagnosis (X-42 years), she experienced butterfly rash and arthralgia. Laboratory studies revealed high antinuclear antibody (ANA) and anti-DNA double-stranded antibody (anti-dsDNA) titer, and hypocomplementemia. Following a renal biopsy, the patient was diagnosed with SLE and lupus nephritis in International Society of Nephrology/ Renal Pathology Society class IV. Oral prednisolone (PSL) was initiated at a dose of 70 mg/day. At X-35 years, PSL was tapered to 10 mg/day, but at X-34 years, lupus nephritis flared and she was treated with a pulse dose of intravenous methylprednisolone (mPSL) 500 mg/day for 3 days. At X-30 years, PSL was tapered to 10 mg/day and maintained at this dose. The patient’s hospital visits paused between X-25 and X-22 because of pregnancy and childbirth. After restarting PSL 10 mg/day, her serum creatinine level increased to 1.7 mg/dl and she
again discontinued her hospital visits between X-15 and X-13 years. At X-13 years, conventional hemodialysis was initiated three times a week because of pulmonary congestion, and the serum creatinine level increased to 8.0 mg/dl. Despite maintenance hemodialysis, the patient’s complement level was low and anti-dsDNA antibody titer remained high, but PSL was tapered to 5 mg/day because of an expected decrease in disease activity. However, the anti-dsDNA antibody did not decrease and the patient was referred to our hospital. PSL 5 mg/day was continued. At X-4 years, the anti-dsDNA antibody titer increased to 7980 IU/ml and the patient experienced phlegmon of the lower limbs and central nervous system lupus. Intravenous mPSL pulse was administered for 3 days followed by PSL 50 mg/day, plasma exchange once, and immunoabsorption seven times. The anti-dsDNA antibody titer subsequently decreased to 600 IU/ml. Intravenous Cyclophosphamide (IVCY) was started as maintenance therapy, but cytopenia developed as a side effect. After additional intravenous mPSL pulses were given, the anti-dsDNA antibody titer decreased to 400–600 IU/ml and PSL was continued at 10 mg/dl. IVCY was subsequently administered three times, but the patient’s cytopenia worsened and the anti-dsDNA antibody titer did not improve. At X-2 years, SLE flared with fatigue, loss of appetite, diarrhea, and an increase in anti-dsDNA antibody titer to 2260 IU/ml. The patient was again admitted to our hospital where she received intravenous mPSL pulses and immunoabsorption followed by mycophenolate mofetil (MMF) 250 mg/day as maintenance therapy. The anti-dsDNA antibody titer decreased to 100 IU/ml, but the patient experienced diarrhea and nausea as a side effect of MMF treatment so this treatment was discontinued. At X-1 years, in April, the patient received immunoabsorption because of an anti-dsDNA antibody titer, which subsequently decreased gradually. PSL was tapered to 6 mg/dl, but the anti-dsDNA antibody titer remained above 200 IU/ml. Figure 1A shows the duration of treatment up to this point. From the following December, amoxicillin and carbocysteine were administered because the patient experienced right exudative otitis media. However, in January at X years, the patient experienced a rash on her entire body, followed by fever the next day. The patient was admitted to our hospital 4 days later where a general examination showed that her height was 1.52 m, body weight 32.4 kg, blood pressure 159/94 mmHg, heart rate 100/min, and body temperature 37.9°C. The patient’s electrocardiogram, chest radiograph,
computed tomography (CT) scan, and antiviral antibody titers showed no significant findings. Treatment with amoxicillin and carbocysteine was discontinued and the rash and fever subsequently disappeared, so a diagnosis of drug-induced rash was made. Regarding the patient’s SLE, the anti-dsDNA antibody and ANA titers were high (200 IU/ml and 1:640, respectively) despite her end-stage renal failure. She had also bicytopenia and low white blood cell (2700/µl) and platelet (9.8 × 10⁴ /µl) counts, but normal neutrophils (1800/µl), lymphocytes (580/µl), hemoglobin (12.1 g/dl), and hypocomplementemia (CH50 30 U/ml, C3 40 mg/dl, C4 8 mg/dl). Her serum gamma globulin level was within the normal range (IgG 1283 mg/dl, IgA 276 mg/dl, IgM 69 mg/dl). Her Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA-SLEDAI) score was 6 and British Islet Lupus Assessment Group (BILAG) index 2004 score was new B and 6. We initiated treatment with belimumab for the following reasons: the patient was opposed to an increase in the dose of PSL because of its side effects; we were also concerned about the side effects of both IVCY and MMF; and we did not anticipate that the patient’s anti-dsDNA antibody and ANA titers would decrease sufficient with only immunoadsorption and low-dose PSL treatment. The patient thus received immunoadsorption four times every 2 days followed by intravenous belimumab 330 mg (10 mg/kg). She experienced no adverse events and was subsequently discharged from hospital. A second dose of belimumab was given 2 weeks after the first dose. The complement level increased after the first dose of belimumab and the anti-dsDNA antibody titer also decrease after 1 month; however, the serum gamma globulin level was maintained within the normal range. The patient’s fatigue resolved, so we considered the treatment as effective for SLE. However, the patient was re-admitted to our hospital 3 weeks later because of pneumocystis carinii pneumonia and congestive heart failure. After these conditions were fully resolved, we decreases the dose of belimumab from 330 mg (10 mg/kg) to 120 mg (4 mg/kg) because of concerns about the risk of re-infection. A third dose of belimumab was given, and the patient’s anti-dsDNA antibody titer decreased to 70 IU/ml. No SLE flare or infection was reported after that. After 7 doses of belimumab, the only reported adverse event was pneumonia and the levels of C3, C4, and anti-dsDNA antibody were 41.1 mg/dl, 9.3 mg/dl, and 301 IU/ml, respectively. The SELENA-SLEDAI score was 4, and the BILAG index 2004 score was no
new A and B, and 1. Figure 1B shows the duration of treatment from X years.

Discussion

The evaluation of disease activity prior to initiating therapy can be challenging in patients with SLE who have started hemodialysis. [8] In our previous report, the most frequent symptoms reported by these patients after initiation of hemodialysis were arthritis, fever, pericarditis, and pleuritis. [9]

Regarding serological evaluation, hematological BILAG activity can be evaluated even after starting hemodialysis. [10] A previous retrospective, case-controlled study showed that hematologic activity, complement 4, anti-cardiolipin IgM, and age at initiation of renal replacement therapy were independent risk factors for extrarenal SLE flares. [11] In our case, although low-grade fever and general fatigue was often the only clinical symptom, the patient was in a prolonged serologically active state as shown by persistent neutropenia, lymphocytopenia, anemia, hypocomplementemia, and high anti-dsDNA antibody titer, with a very high possibility of major flare up.

There are few reports on the treatment of patients with SLE who show activity even after initiation of dialysis. [8, 12] Prednisolone represents the mainstay of treatment of SLE, regardless of whether the patient is on dialysis. Side effects such as infections, osteoporosis, and cardiovascular events are managed by immediate tapering of prednisolone tapering to approximately 5 mg/day. [13] Given that patients on hemodialysis are susceptible to infection, osteoporosis, and cardiovascular events even without prednisolone therapy, we kept the prednisolone dose to a minimum in our case. [14 15]

Furthermore, the survival rate in patients with ESRD treated with prednisolone alone is surprisingly similar to that in patients who receive no medication, suggesting that low-dose prednisolone treatment may be inadequate for this patient population, and combined use with an immunosuppressant is recommended. [12] However, no intradialytic clearance with hemodialysis is observed with the use of immunosuppressive agents, other than azathioprine and cyclophosphamide. [16 17] Given that improvements in non-renal disease were observed in the aspreva lupus management study (ALMS), we used cyclophosphamide and MMF as induction and maintenance therapy combined with immunoadsorption therapy in the present case. [18 19] However, leukopenia and frequent diarrhea are associated with cyclophosphamide and MMF, respectively, despite the use
of a dialysis dose, so we decided to administer a biological agent that could be used independently of renal function.

Currently, belimumab is covered by health insurance in Japan for the treatment of SLE as a biological agent targeting B cells. BAFF is an important regulator of B-cell survival and function, and in BAFF-overexpressing mice, SLE-like pathological conditions are induced such as the appearance of anti-dsDNA antibody and the deposition of immune complex to the kidney. [20] BAFF levels are increased in patients with SLE, and are reported to be correlate positively with anti-dsDNA antibody titer. [21] Belimumab, as an anti-BAFF antibody, is therefore used to treat active SLE, especially in patients with a high anti-dsDNA antibody titer and low serum complement level. [22] However, B-cell distribution in patients with ESRD shows a decrease in all B-cell subpopulations except transitional B cells without belimumab administration. In ESRD, BAFF receptor expression on B cells is decreased because of uremia, which causes a reduction in total B cells. [23, 24] These specific findings to ESRD patients led us to following hypothesis. (1) The so-called ‘burnout’ phenomenon of SLE with ESRD was presumed in the case of a patient with autoreactive B cells in the B-cell subpopulations reduced by uremia. (2) Diffuse reduction of B-cell subpopulations results in a high concentration of BAFF via a positive feedback mechanism in patients with ESRD even if it is not in patients with SLE. In summary, in ESRD patients with SLE, there is no significant decrease in transitional B cells, while BAFF is elevated. [23]

The main target cells of belimumab are transitional B cells, which are antigen-unprimed mature B cells that have recently emerged from bone marrow to a secondary lymphoid organ, and follicles and marginal zone B cells, which is classified as mature B cells. Because Belimumab acts on both insensitive naïve B cells and transitional B cells in uremic patients to attenuate the activity of SLE, and a synergistic immunological effect can be expected in patients with ESRD. (Fig. 2) Moreover, in recent years, belimumab has been reported to act on transitional B cells to induce negative selection of autoreactive B cells. [22] In the present case, the anti-dsDNA antibody titer decreased and the complement value increased immediately after the administration of belimumab. In contrast, a very small decrease in serum IgG was observed. According to previous reports, a belimumab-induced reduction in anti-dsDNA antibody titer was attributed to loss of naïve B cells and transitional B cells,
and secondary loss of memory B cells and plasma cells. Given the secondary effect, anti-dsDNA antibody titer reduction frequently is low in magnitude and takes a considerable amount of time. [25] However, previous reports have shown that naïve activated B cells from patients with active SLE can directly give rise to plasmablasts. [22, 26] Although plasmablasts are short-lived, they have the ability to produce antibodies, and belimumab may have a role in this process. [27] Finally, the side effects of belimumab treatment should be considered. In the BLISS52 and BLISS76 trials, large double-blind studies with belimumab, no significant difference was observed in the incidence of serious infections between a belimumab 10 mg/kg group and a placebo group. [28 29] In the present case, after 4 weeks of administration of belimumab 10 mg/kg, lymphocytes were significantly reduced and Pneumocystis carinii pneumonia occurred. The patient improved immediately after treatment, but increased apoptosis of naïve and central memory CD4 + T cells caused by uremia may have caused the reduction in lymphocytes. [30 31] We subsequently reduced the dose of belimumab to 4 mg/kg to reduce the incidence of side effects in a reference clinical trial to determine the biological activity and safety of belimumab in patients with SLE. [32] Despite the reduction in belimumab, particular attention should be paid to infection because belimumab and uremia synergistically suppress B-cell lineage via different pathways. Currently, in this case, the treatment can be continued and has a favorable treatment course. However, a major limitation of this study is the short observation period. In conclusion, belimumab may represent a good treatment option for patients with SLE, even after initiation of dialysis. However, in patients with uremia requires careful follow-up also in these patients as it may enhance the side effects of belimumab.

Abbreviations
SLE: Systemic lupus erythematosus; ESRD: End stage renal disease; BAFF: B cell activating factor; ANA: Antinuclear antibody; IVCY: Intravenous cyclophosphamide; MMF: Mycophenorate mofetil; CT: Computed tomography; Ani-dsDNA antibody: anti-DNA double straded antibody; ISN/RPS: International Society of Nephrology/ Renal Pathology Society; PSL: prednisolone; mPSL: Methyl prednisolone; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index; BILAG: British Islet Lupus Assessment Group; ALMS: Aspreva lupus
management study

Declarations

**Ethics approval and consent to participate:** Ethics approval to publish a case report is not needed from our institute. (Tokyo Women’s Medical University)

**Consent for publication** The authors obtained written consent from patient for the publication of the data.

**Availability of data and materials:** All data concerning the case is presented in the manuscript.

**Competing Interests:** All authors have no conflicts of interest to declare.

**Funding:** Not applicable

**Authors’ contribution:** KK was the corresponding author responsible for the writing of the article.

SO treated the patients and wrote the manuscript. WO, Al, MS, YY, MK, MT, YU, MS and KU treated and managed the patient. NS, TT, YM, YI, and KA undertook the literature search. TM and KN participated in the care of the patient. All of the authors read and approved the final manuscript.

**Acknowledgments:**

We thank Clare Cox, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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Table
Due to technical limitations, the table is only available as a download in the supplemental files section.

Figures
Figure 1

A) The results of laboratory examinations and the course of treatment from X-9 years to X-1.

B) The results of laboratory examinations and the course of treatment from X years.
A) The results of laboratory examinations and the course of treatment from X-9 years to X-1. B) The results of laboratory examinations and the course of treatment from X years.

Figure 2

Shematic Diagram of the effect of uremia and belimumab in B cell lineage
Figure 2

Shematic Diagram of the effect of uremia and belimumab in B cell lineage

Supplementary Files

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