Effectiveness of Belimumab for Glucocorticoid Discontinuation in Juvenile-Onset Lupus Nephritis

Abstract

Lupus nephritis (LN) is an important complication of systemic lupus erythematosus, for which glucocorticoids (GCs) are the primary treatment. Due to the side effects associated with GCs, their long-term use should ideally be tapered and discontinued. At present, no such possibility exists without problematic flares after discontinuation. We administered belimumab, a human monoclonal antibody that binds to a soluble B lymphocyte stimulator to reduce the number of activated B cells, to six patients with Type IV LN to discontinue GCs. The six patients were 10–15 years old when LN developed and 15–24 years old when belimumab treatment was initiated. Prednisolone was tapered from 6 to 20 mg by 2.5–5 mg every month until the dosage reached 5 mg, at which point the dosage was further reduced by 1 mg every 6 months. One patient was transferred to another hospital midway and five patients discontinued GCs. No flares occurred 8–38 months post discontinuation. No adverse effects were observed following belimumab treatment. In conclusion, belimumab was effective in the successful discontinuation of GCs.

Keywords: *Systemic lupus erythematosus, Lupus nephritis, Belimumab, Glucocorticoid discontinuation*

Introduction

Lupus nephritis (LN) is a major complication occurring in 40% of patients with systemic lupus erythematosus (SLE).[1] Glucocorticoids (GCs) are the cornerstone treatment for SLE. Although GC use in the long term should ideally be discontinued owing to the associated side effects, such as cataracts, psychiatric disorders, osteoporosis, cardiovascular disease, and infection,[2,3] no safe method currently exists. Belimumab is a human monoclonal antibody that binds to a soluble B lymphocyte stimulator to reduce the number of activated B cells and is effective in treating severe LN.[1] We administered belimumab following GC discontinuation in patients with LN.

Case Series

Belimumab was administered to six patients diagnosed with LN Type IV between 2006 and 2016. All patients received nine sets of methylprednisolone pulse therapy (MPT) and mycophenolate mofetil (MMF) as induction therapy. Patients achieved remission and received maintenance therapy for 3–12 years before starting belimumab therapy. Maintenance therapies included prednisolone, MMF, tacrolimus (Tac), and hydroxychloroquine (HCQ). Belimumab was administered during 2017–2019 at a dosage of 10 mg/kg on days 1, 15, and 29, and subsequently once every 4–5 weeks. Prednisolone reduction was initiated after clinical remission; three cases were serologically active clinically quiescent (SACQ). Prednisolone was tapered from an initial dosage of 6–20 mg by 2.5–5 mg every month until reaching a dosage of 5 mg. Subsequently, the dosage was reduced by 1 mg every 6 months. Flares were defined using the SELENA-SLEDAI Flare Index.[4] One patient was transferred to the adult department during follow-up, and five patients underwent continuous therapy [Table 1]. No cases of severe hypersensitivity reaction, infection, progressive multifocal leukoencephalopathy, interstitial pneumonia, or depression, which are known side effects of belimumab, were observed.

Case 1

A 22-year-old female presented with two flares and herpes zoster in the 2 years before starting intravenous belimumab following 6 years of remission. Two years later, one flare occurred (worsening of serum creatinine, complement, and urinary protein levels). No flares occurred 3 years after belimumab treatment, and prednisolone was discontinued. HCQ was then initiated. No flares occurred for 36 months after prednisolone discontinuation.

Case 2

A 24-year-old female had persistent proteinuria (urine protein-to-creatinine ratio: 1.0–1.5 g/gCr) for 2 years before receiving subcutaneous belimumab. She remained in remission for 3 years after experiencing two flares over 7 years. One year after belimumab treatment, proteinuria normalized, and 20 months later, belimumab was changed to intravenous injection due to puncture pain. No flares occurred for 30 months after prednisolone discontinuation.

Case 3

An 18-year-old female had no flares before receiving subcutaneous belimumab. The belimumab administration method was changed to intravenous injection to avoid puncture pain after 3 months. No flares occurred for 31 months after prednisolone discontinuation.

Case 4

A 21-year-old female presented with thrombocytopenia before receiving subcutaneous belimumab. Nine months later, the prednisolone dose was reduced from 15 to 5 mg. The platelet counts stabilized, and no flares occurred for 22 months after prednisolone discontinuation.

Table 1: Characteristics of patients before prednisolone reduction and renal function at the final observation

Patient no.	Onset age	Belimumab starting age	Drug at starting belimumab	Months of clinical remission before PSL reduction	Reason for starting belimumab	PSL side effects	PSL reduction status	Last eGFR (ml/min/1.73-m^2)
1	15	22	PSL 20 mg MMF 750 mg Tac 1.5 mg	14	Suppression of lupus nephritis flare	Osteoporosis	SACQ	106
2	12	24	PSL 7.5 mg MMF 1000 mg Tac 4 mg HCQ 300 mg	8	Improvement of proteinuria	None	CR	117
3	14	18	PSL 6 mg MMF 500 mg HCQ 300 mg	36	Discontinuation of PSL	None	CR	146
4	14	21	PSL 15 mg MMF 1000 mg HCQ 400 mg	4	Improvement of thrombocytopenia	None	SACQ	96
5	10	15	PSL 10 mg MMF 1000 mg	6	Improvement of non-adherence, suppression of lupus nephritis flare	Short stature	SACQ	143

PSL: Prednisolone, eGFR: Estimated glomerular filtration rate, MMF: Mycophenolate mofetil, Tac: Tacrolimus, HCQ: Hydroxychloroquine, SACQ: Serologically active clinically quiescent.

Case 5

A 15-year-old boy experienced one flare due to drug neglect following 3 years of remission. After intravenous belimumab administration, the dose of prednisolone was reduced from 10 to 4 mg over 6 months. Three months after the prednisolone dose was reduced to 1 mg, the patient experienced a flare (worsening of serum creatinine, complement, and urine protein levels). After MPT, the prednisolone dose was reduced from 30 to 5 mg over 6 months, and then to 0 mg over the next year. No flares occurred for 8 months after prednisolone discontinuation, and the patient was transferred to the adult department.

Discussion

In five cases of LN, prednisolone was discontinued after administering belimumab, and no flares occurred 8–38 months after prednisolone discontinuation. Renal function was normal in all patients. Some reports suggest that prednisolone should not be discontinued but maintained at 7.5 mg or less[5] or 5 mg or less.[6] However, considering their side effects, GCs should be discontinued as much as possible. Factors that suppress relapse include maintenance of remission for >5 years[7] and intensive treatment (induction with MPT and maintenance with MMF and/or Tac).[8] Risk factors for relapse include SACQ,[7,9] history of LN,[7] and age under 40 years.[9] In our cases, three patients had SACQ, remission period was <3 years, and the age at prednisolone discontinuation was <27 years. In Cases 1 and 5, the flare could not be suppressed, even with intensive treatment; as side effects of prednisolone were also observed, prednisolone was discontinued despite SACQ. Belimumab resulted in complete remission and long-term prevention of flares. Belimumab should be administered in cases where conventional therapy does not result in sustained remission.

Reports on how to reduce prednisolone include immediate discontinuation from 5 mg, which increases the flare risk by four-fold compared with the maintenance group,[10] and gradual prednisolone discontinuation from 5 mg over 12–24 months, which reduces the flare risk.[9] In this study, prednisolone was discontinued over 2.5 years; however, the dose could have been reduced at a faster rate.

Belimumab was effective for discontinuing GCs in cases of LN. Further studies with more patients are needed to validate our results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

Tomoo Kise[1], Masatsugu Uehara[1]

[1]Division of Pediatric Nephrology, Okinawa Prefectural Nanbu Medical Center, Children's Medical Center, Haebaru, Japan

Corrresponding author:
Tomoo Kise, Division of Pediatric Nephrology, Okinawa Prefectural Nanbu Medical Center, Children's Medical Center, Haebaru, Japan.
E-mail: tomookise0618@gmail.com

References

1. Plüß M, Piantoni S, Tampe B, Kim AHJ, Korsten P. Belimumab for systemic lupus erythematosus - Focus on lupus nephritis. Hum Vaccin Immunother 2022;18:2072143.
2. Enríquez-Merayo E, Cuadrado MJ. Steroids in lupus: Enemies or allies. J Clin Med 2023;12:3639.
3. Fanouriakis A, Kostopoulou M, Andersen J, Aringer M, Arnaud L, Bae SC, *et al*. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis 2024;83:15-29.
4. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, *et al*. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8.
5. Hao Y, Ji L, Gao D, Fan Y, Geng Y, Zhang X, *et al*. Flare rates and factors determining flare occurrence in patients with systemic lupus erythematosus who achieved low disease activity or remission: Results from a prospective cohort study. Lupus Sci Med 2022;9:e000553.
6. Floris A, Chessa E, Sebastiani GD, Prevete I, Iannone F, Coladonato L, *et al*. Glucocorticoid tapering and associated outcome in patients with newly diagnosed systemic lupus erythematosus: The real-world GULP prospective observational study. RMD Open 2022;8:e002701.
7. Fasano S, Coscia MA, Pierro L, Ciccia F. Which patients with systemic lupus erythematosus in remission can withdraw low dose steroids? Results from a single inception cohort study. Lupus 2021;30:991-7.
8. Nishi K, Ogura M, Ishiwa S, Kanamori T, Okutsu M, Yokota S, *et al*. Glucocorticoid discontinuation in pediatric-onset systemic lupus erythematosus: A single-center experience. Pediatr Nephrol 2022;37:2131-9.
9. Ji L, Gao D, Hao Y, Huang H, Wang Y, Deng X, *et al*. Low-dose glucocorticoids withdrawn in systemic lupus erythematosus: A desirable and attainable goal. Rheumatology (Oxford) 2022;62:181-9.
10. Mathian A, Pha M, Haroche J, Cohen-Aubart F, Hié M, Pineton de Chambrun M, *et al*. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: A randomised clinical trial. Ann Rheum Dis 2020;79:339-46.

How to cite this article: Kise T, Uehara M. Effectiveness of Belimumab for Glucocorticoid Discontinuation in Juvenile-Onset Lupus Nephritis. Indian J Nephrol. 2025;35:85-7. doi: 10.25259/IJN_444_2024

Received: 05-08-2024; **Accepted:** 20-08-2024; **Online First:** 04-10-2024; **Published:** 04-01-2025

DOI: 10.25259/IJN_444_2024

Insights into Therapeutic Strategies and Longitudinal Outcomes: A Retrospective Analysis of NELL1 Positive Membranous Nephropathy Cohort

Abstract

Membranous nephropathy (MN) is a rare autoimmune disease, in which the circulating autoantibodies against antigens attack podocytes. Neural Epidermal Growth Factor like 1 (NELL1) 1-associated MN is the second most common antigen, following phospholipase A2 receptor. Complementary and alternative medicine and malignancies play a pivotal role in the development of NELL1-MN. This retrospective study describes the clinical characteristics, therapeutic strategies, and longitudinal outcomes in patients with NELL1-MN at our center.

Keywords: *Membranous nephropathy, NELL1, PLA2R, Complementary and alternative medicine, CNI*

Introduction

Membranous nephropathy (MN) is a rare autoimmune disease, in which circulating autoantibodies against antigens attack podocytes. It accounts for about 20% cases of nephrotic syndrome in adults.[1] Sethi *et al.* using laser microdissection and tandem mass spectrometry (MS/MS) have recently described six new target antigens in MN that include neural tissue encoding protein with EGF-like repeats [Neural Epidermal Growth Factor like 1 (NELL1)] and others like Exostosin-1, Semaphorin3B.[2] NELL1 is the second most common antigen implicated in development of MN.[3] Emerging evidence suggests that complementary and alternative medicine (CAM) and malignancies may play a pivotal role in the development of NELL1-associated MN (NELL-1 MN).[4-6] Many cases of NELL-MN remit following stoppage of the offending agent but some may require immunosuppression. We examined the clinical characteristics, therapeutic strategies, and longitudinal outcomes of NELL1-MN patients at our center.

Case Series

All adult cases with NELL1-MN diagnosed in Nephrology Department of Sawai Man Singh Medical College & Hospital, Jaipur, India between April 1, 2021 and March 31, 2023 were identified from hospital records and contacted via telephone. Data on demographic parameters, biochemical, and histological characteristics were collected. Immunosuppression and treatment history along with baseline and last available serum albumin, creatinine, and proteinuria were recorded. Those with CKD stage 3 or above at presentation, patients with lupus nephritis or other connective tissue disorders were excluded.