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Single Case

Telitacicept Treatment Refractory Lupus Nephritis: A Case Report

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Keywords
Systemic lupus erythematosus · Refractory lupus nephritis · Telitacicept · Biologics · Treatment

Abstract
Introduction: Refractory lupus nephritis (LN) causes kidney disease progression and increases the risk of loss of renal function. Due to the high specificity and few side effects of biological agents, they are recommended for the treatment of systemic lupus erythematosus. There are few data on telitacicept for the treatment of refractory LN. ***Case Presentation:*** Here, we report the efficacy and safety of telitacicept in the treatment of refractory LN in a 25-year-old female patient. This patient with refractory lupus developed *Pneumocystis jirovecii* pneumonia while using multitargeted therapy, and the patient's urine protein was rapidly relieved after telitacicept combination with low-dose mycophenolate mofetil (MMF). ***Conclusion:*** This result suggests that telitacicept has a positive effect on refractory LN with no significant side effects. Further reports and a registry are necessary to confirm that telitacicept with low-dose MMF should be preferred in refractory LN.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs, including the skin, joints, kidneys, lungs, central nervous system, and hematopoietic system. Kidney is one of the most important visceral organs involved in SLE. Although only approximately 50% of patients with SLE develop clinically evident renal disease, almost all patients have some degree of renal involvement demonstrated by biopsy studies [1]. The pathogenesis of SLE is not yet fully understood. However, aberrant activation of autoreactive B and T cells, antigen misidentification, and excessive autoantibody production are important in the pathogenesis of SLE [2]. Among them, B-lymphocyte stimulating factors (B-lymphocyte stimulator [BLyS]) and A proliferation-inducing ligand (APRIL) are key factors in maintaining the B-cell repertoire and humoral immunity [3]. Although glucocorticoids and immunosuppressants have achieved significant clinical efficacy in treating lupus nephritis (LN), biologics have made significant breakthroughs in the treatment of immune diseases for refractory cases over the past 2 decades [4]. A variety of biologics have been developed as potential therapeutic targets for SLE [5]. Telitacicept, a novel recombinant fusion protein, is a BLyS/APRIL dual-target biological inhibitor that inhibits the development and survival of mature B cells, which has been approved for the treatment of SLE in China [3]. However, there are few data on telitacicept for the treatment of refractory LN. This article reports the efficacy and safety of telitacicept for the treatment of refractory LN in adults. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538033).

Case Report

A 25-year-old woman was admitted to a local hospital 2 years ago because of facial and lower limb edema. On admission, the patient had abnormal renal function with serum creatinine 150 μmol/L (normal range: 41.00–81.00 μmol/L) and 24-h urine protein excretion was 12.77 g. Laboratory examination showed positive ANA, anti-double-stranded DNA (dsDNA), anti-Sm antibody, anti-U1RNP antibody, and mild reduction of complement C3. Renal histopathology indicated LN (class IV + V); the activity index was 9, and the chronic index was 1. Methylprednisolone (500 mg/day) pulse therapy was administered thrice. Subsequently, multitarget treatments were administered, including prednisone 30 mg/day, mycophenolate mofetil (MMF) 1,000 mg/day, and tacrolimus 2 mg/day. After treatment for 4 months, anti-dsDNA and anti-ANA antibodies were negative, serum creatinine decreased from 150 μmol/L to 73 μmol/L, and the urine protein-to-creatinine ratio decreased from 5,665 mg/gCr to 3,526 mg/gCr. Due to concerns about infection, MMF was stopped, and tacrolimus was adjusted to 4 mg/day, combined with hydroxychloroquine (HCQ) (200 mg/day). After 6 months of therapy, the patient's urine protein-to-creatinine ratio and serum albumin (ALB) were in a range of 3,834.33–8,590.89 mg/gCr and 22.7–32.8 g/L, respectively. In the seventh month of treatment, the patient developed fever and cough, procalcitonin (PCT) and C-reactive protein (CRP) levels increased, and cytomegalovirus (CMV)-IgM was positive. Chest CT and blood next-generation sequencing results suggested that the patient had *Pneumocystis jirovecii* pneumonia. Tacrolimus and prednisone were discontinued and methylprednisolone (8 mg/day) was administered. The piperacillin-tazobactam (13.5 g/day), sulfamethoxazole-trimethoprim (3.84 g/day), and ganciclovir (0.5 g/day) were given to treat the lung infection. After 2 months, the patient's lung infection was in remission. However, the patient's urine protein level was still within the nephrotic-range proteinuria. At the ninth month of treatment, the patient was treated with 160 mg per week telitacicept for 8 weeks.

Telitacicept was administered in combination with MMF (500 mg/day), HCQ (200 mg/day), and prednisone (10 mg/day). After 8 weeks (eleventh month) of telitacicept treatment, the urine protein-to-creatinine ratio reduced from 5,600 to 3,856 mg/gCr. Serum ALB increased from 30.9 to 38.9 g/L and serum creatinine was stable. Level of immunoglobulin G decreased from 3.76 to 2.91 g/L. Then telitacicept reduced to 80 mg once per week. After 4 months (fifteenth month) of telitacicept therapy, the urine protein-to-creatinine ratio reduced significantly from 3,856 to 1,376 mg/gCr. Serum ALB improved from 38.9 to 42 g/L and level of immunoglobulin G increased from 2.91 to 4.21 g/L. After 6 months of telitacicept treatment (fifteenth month), the urine protein-to-creatinine ratio reduced significantly from 5,600 to 1,376 mg/gCr. During follow-up (from ninth to twenty-first month), the patient's renal function and proteinuria were stable, and there were no apparent manifestations of infection (Fig. 1).

Discussion

In this case, the patient achieved partial remission in active parameters of lupus by classic immunosuppressor MMF and tacrolimus, including serum autoantibodies changing to negative and complement C3 increasing. However, proteinuria was still massive, and even worse, severe opportunistic pulmonary infection occurred. Considering the previous *Pneumocystis jirovecii* pneumonia and CMV infection, telitacicept was administered in combination with MMF (500 mg/day), HCQ (200 mg/day), and prednisone (10 mg/day) for 8 weeks. Urine protein excretion was reduced significantly after 8 weeks of therapy. Then the dose of telitacicept was adjusted to half the amount (80 mg per week). After 6 months of treatment, the urine protein level decreased significantly in the patient. During telitacicept treatment, no pulmonary infections or adverse effects were observed. SLE is an autoimmune disorder characterized by multisystem microvascular inflammation and the presence of numerous autoantibodies. LN in SLE patients is the second most common cause of death in SLE patients in China [6]. Patients with proliferative LN need to receive induction therapy and maintenance therapy. Multitarget induction therapy with a triple immunosuppressive regimen that includes low dosages of tacrolimus, MMF, and glucocorticoids is reserved for patients with refractory or conventional therapy [7]. Although multitarget treatment for refractory lupus is effective, infection needs to be noticed during treatment.

There is no uniform definition of refractory LN. However, many articles define criteria for refractory LN, such as refractory to standard treatments, or failure of immunosuppressive drugs [4]. The guidelines of the American College of Rheumatology have defined refractory LN as worsening nephritis by 3 months or treatment failure as assessed by treatment at 6 months [8]. According to the European League Against Rheumatism (EULAR/ERA-EDTA) criteria, refractory LN was defined as those patients who had no partial response after 6–12 months of treatment [9]. At the time of 4 months of multitarget therapy, the proteinuria was still at the level of nephrotic syndrome, and we defined the patient as refractory LN. Many therapeutic strategies may be used for patients with refractory LN, including alternative first-line induction drugs (switching from cyclophosphamide to MMF or vice versa), calcineurin inhibitors, and biological therapeutics. Recently, because of the high specificity and few side effects of biological agents, the biologicals are recommended for the treatment of refractory LN [10–12].

Previous studies have found that abnormal activation of B lymphocytes is involved in the progression of LN, which produces a large number of immune complexes and deposits in the kidney [2]. BLyS and APRIL are key survival cytokines for B-cell survival and development. They bind to three receptors: transmembrane activator and calcium-modulating cytophilic

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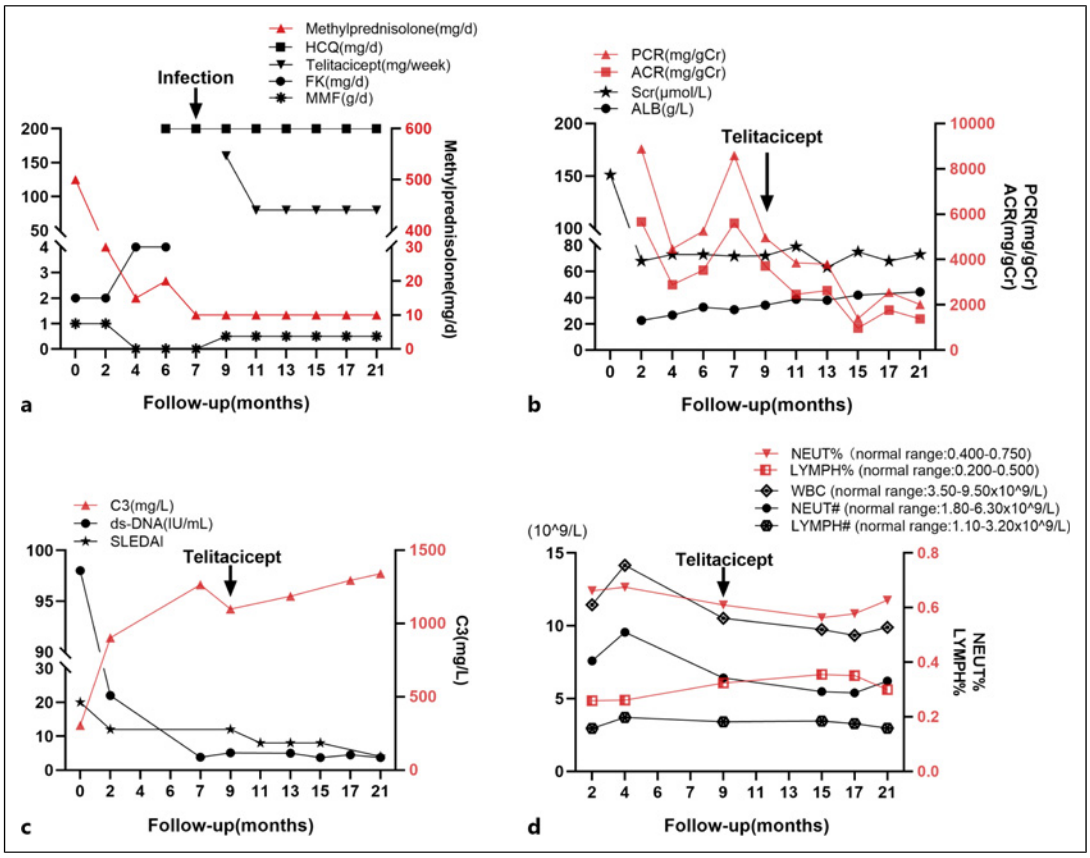

Fig. 1. Changes in the course of drug treatment and clinical indicators of patients. **a** The patient was treated with medication. **b** After treatment, the patient showed reduced ACR and PCR results. Albumin level increased and serum creatinine was stable. **c** The patient's C3 level increased, and SLEDAI, dsDNA values improved. **d** Changes in white blood cell, lymphocyte, and neutrophil counts were observed during the therapy period. HCQ, hydroxychloroquine; FK, tacrolimus; MMF, mycophenolate mofetil; C3, complement 3; Scr, serum creatinine; ALB, albumin; SLEDAI, systemic lupus erythematosus disease activity index; dsDNA, double-stranded DNA; PCR, protein-to-creatinine ratio; ACR, albumin-to-creatinine ratio; WBC, white blood cell; NEUT, neutrophil; LYMPH, lymphocyte.

ligand interactor (TACI), B-cell maturation antigen, and BAFF receptor. Among SLE patients, APRIL and BLyS levels increased, and they were positively correlated with SLE disease activity and organ damage [13]. Novel drugs for reducing autoantibody formation in SLE include monoclonal antibodies that modulate or deplete B cells (anti-CD22 and anti-CD20 antibodies, respectively), or that interfere with the stimulatory effects of the soluble factor B-lymphocyte stimulator (anti-BLyS antibodies, belimumab). Blocking costimulatory molecule interactions, such as the CD40-CD40 ligand interaction (CTLA-4)-IgG1 (abatacept), has also been attempted as a therapeutic strategy for SLE. Alternative approaches include using atacicept and telitacicept, a modulator ligand interactor (TACI)-Ig fusion protein, or tolerogens, such as abetimus [14]. Telitacicept is a recombinant fusion protein comprising the extracellular domain of the TACI receptor and the human IgG1-Fc domain. Telitacicept blocks B-cell stimulation by both the BLyS and APRIL pathways. In animal experiments, treatment with TACI-Fc targeting APRIL and BLyS resulted in a reduction in dsDNA levels and renal pathological scores. Studies have shown that patients with SLE could gain a response rate of 71% for the systemic lupus erythematosus response index 4 (SRI-4) after receiving

telitacicept 80 mg per week from the complete analysis set, which was 37.1% higher than that in the placebo group [15]. A small sample clinical study on refractory LN in children indicated that telitacicept plus standard treatment could significantly improve the SRI-4 response rate [16]. Recently, Chen et al. [17] reported the treatment of a patient with refractory proliferative LN with telitacicept. The patient is treated with the combination of steroids (5 mg per day), HCQ (400 mg per day), MMF (0.5–1.0 g per day), and telitacicept (160 mg once per week). At 19 months follow-up, massive proteinuria was controlled. The telitacicept combination with traditional immunosuppressants could reduce proteinuria and improve remission of refractory proliferative LN [18, 19]. We reported the patient with LN developed a pulmonary infection after immunosuppressive drugs; then telitacicept plus low-dose MMF were given. The patient had rapid remission of proteinuria and no secondary infection. The results suggested that telitacicept combined with MMF had certain advantages in refractory LN.

Conclusions

As a new biological agent with the dual target of APRIL and BLyS, telitacicept combination with low-dose MMF has a positive effect on refractory LN with no significant side effects.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local guidelines. This study protocol was reviewed and the need for approval was waived by Ethics Committee of Guangdong Provincial People's Hospital. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Shuangxin Liu and Lixia Xu designed this study. Sijia Li and Shuting Deng were responsible for the data collection and analysis and wrote the manuscript. Sichun Wen, Siqi Peng, Nan Jiang, Bohou Li, Boxi Chen, Ye Yuan, Qiong Wu, Yiming Tao, Jianchao Ma, Ting Lin, Feng Wen, Zhuo Li, Hao Dai, Renwei Huang, Zhonglin Feng, and Zhilian Li contributed to the follow-up study. Shuangxin Liu and Lixia Xu served as lead medical writers and illustrators for this manuscript. All the authors reviewed the manuscript and signed off on its accuracy.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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