Tohoku J. Exp. Med., 2022, **258**, 219-223

Telitacicept for Recalcitrant Cutaneous Manifestations of Systemic Lupus Erythematosus: A Case Report and Review of the Literature

Xinyue Ma,[1,*] Xiaoying Fu,[2,*] Beibei Cui[3] and Hui Lin[3]

[1]West China School of Medicine, Sichuan University, Chengdu, Sichuan, China
[2]Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[3]Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Telitacicept is a novel humanized, recombinant transmembrane activator and calcium modulator and cyclophilin ligand interactor and the Fc portion (TACI-Fc) fusion protein, designed to neutralize the activity of both B-cell lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL). On March 9, 2021, telitacicept received its first approval in China for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE). Additionally, on April 15, 2020, the U.S. Food and Drug Administration (FDA) granted fast track designation to telitacicept for the treatment of SLE. Clinical studies of telitacicept in several other indications, including IgA nephropathy, multiple sclerosis, myasthenia gravis, neuromyelitis optica spectrum disorders, rheumatoid arthritis and Sjögren's syndrome are underway in China. This is the first case that reports telitacicept successfully treated a SLE patient with refractory cutaneous involvement, which provides a potential therapeutic option for recalcitrant cutaneous manifestations of SLE. Furthermore, we review reported studies of BLyS targeted treatments for mucocutaneous lupus. Telitacicept appears to have activity in refractory cutaneous involvement of SLE and clinical trials are warranted to further assess this potential therapy.

Keywords: APRIL; B-cell lymphocyte stimulator; refractory cutaneous manifestations; systemic lupus erythematosus; Telitacicept
Tohoku J. Exp. Med., 2022 November, **258** (3), 219-223.
doi: 10.1620/tjem.2022.J074

Introduction

Cutaneous manifestations are frequent, occurring in approximately 80% of patients with systemic lupus erythematosus (SLE) (Durcan et al. 2019). In some refractory cases, B cell targeted biologics, such as rituximab (RTX) and belimumab, have been reported to be efficacious (Fernández-Nebro et al. 2012; Torrente-Segarra et al. 2021).

Telitacicept (RC-18, RCT-18; RemeGen, Yantai, Shandong, China) is a novel humanized, recombinant transmembrane activator and calcium modulator and cyclophilin ligand interactor and the Fc portion (TACI-Fc) fusion protein, designed to neutralize the activity of both B-cell lymphocyte stimulator [BLyS, also known as the B-cell activation factor (BAFF)] and a proliferation-inducing ligand (APRIL) (Dhillon 2021). On March 9, 2021, telitacicept was granted conditional marketing approval by the Chinese National Medical Products Administration (NMPA) for the treatment of adult patients with active, autoantibody-positive SLE. On April 15, 2020, the U.S. Food and Drug Administration (FDA) granted fast track designation to telitacicept for the treatment of SLE.

We report a SLE patient with refractory cutaneous manifestations who was successfully treated with telitacicept.

Case Presentation

A 39-year-old woman was admitted to Rheumatology

Received June 30, 2022; revised and accepted August 21, 2022; J-STAGE Advance online publication September 1, 2022
*These two authors contributed equally to this work.
Correspondence: Hui Lin, M.D., Ph.D., Department of Rheumatology and Immunology, West China Hospital, Sichuan University, No. 37 Guoxue Xiang, Chengdu, Sichuan 610041, China.
e-mail: lhacd@163.com

and Immunology Department for recurrent erythema. Nine years ago, the patient who suffered from erythema and joint pain was diagnosed with SLE and was treated with prednisone, hydroxychloroquine sulfate and leflunomide. The erythema showed no improvement, so leflunomide was replaced by methotrexate. During the next one year, the symptoms recurrently attacked. Methotrexate was replaced by mycophenolate mofetil, and the symptoms finally achieved remission. Seven years ago, for economic reasons, mycophenolate mofetil was replaced by methotrexate.

Three years before this admission, the patient suffered from alopecia areata. One year ago, when prednisone was tapered to a dose of 7.5 mg once daily, the symptoms, including erythema, oral ulcers and joint swelling relapsed. The patient was admitted into our department. Laboratory examinations showed positive anti-dsDNA antibodies (1:32) and positive urine protein (4.7 g/L). The patient was treated with methylprednisolone (24 mg once daily), hydroxychloroquine and leflunomide. The erythema aggravated, so leflunomide was replaced by mycophenolate mofetil (750 mg once daily). Then methylprednisolone was gradually tapered to a dose of 12 mg once daily. One month before this admission, the erythema relapsed.

Physical examinations showed erythema spread over her face and hands. Laboratory examination showed positive antinuclear antibodies (1:320), positive anti-RNP antibodies, and positive anti-Ro-52 antibodies. Anti-dsDNA antibodies were negative. Complement 3 (C3) was 0.7 g/L, and complement 4 (C4) was 0.179 g/L. Urine protein was 0.09 g/24 h. Liver function, kidney function, blood count and urine test were normal. After considering the patient's clinical manifestation and economic conditions, the patient was treated with telitacicept (160 mg once weekly) after being fully informed of the risks associated with it, combined with previous treatment.

The addition of belimumab improved the signs and symptoms of refractory cutaneous lupus. Impressive clinical improvement was seen as early as 4 weeks after initiation of therapy. We were able to document pictorial evidence of improvement as well demonstrating significant change in laboratory examinations result like C3 and C4 level (Fig. 1). Methylpredisolone was tapered to a dose of 10 mg once daily during the follow-up.

All experiments were performed in compliance with the relevant laws. This study was approved by the Biomedical Research Ethics Committee of our hospital and complied with the mandate of the Declaration of Helsinki (2013 edition). The reported patient provided her written informed consent.

Discussion

We report a SLE patient who suffered from refractory cutaneous involvement and was effectively treated with telitacicept after failure to methotrexate, mycophenolate

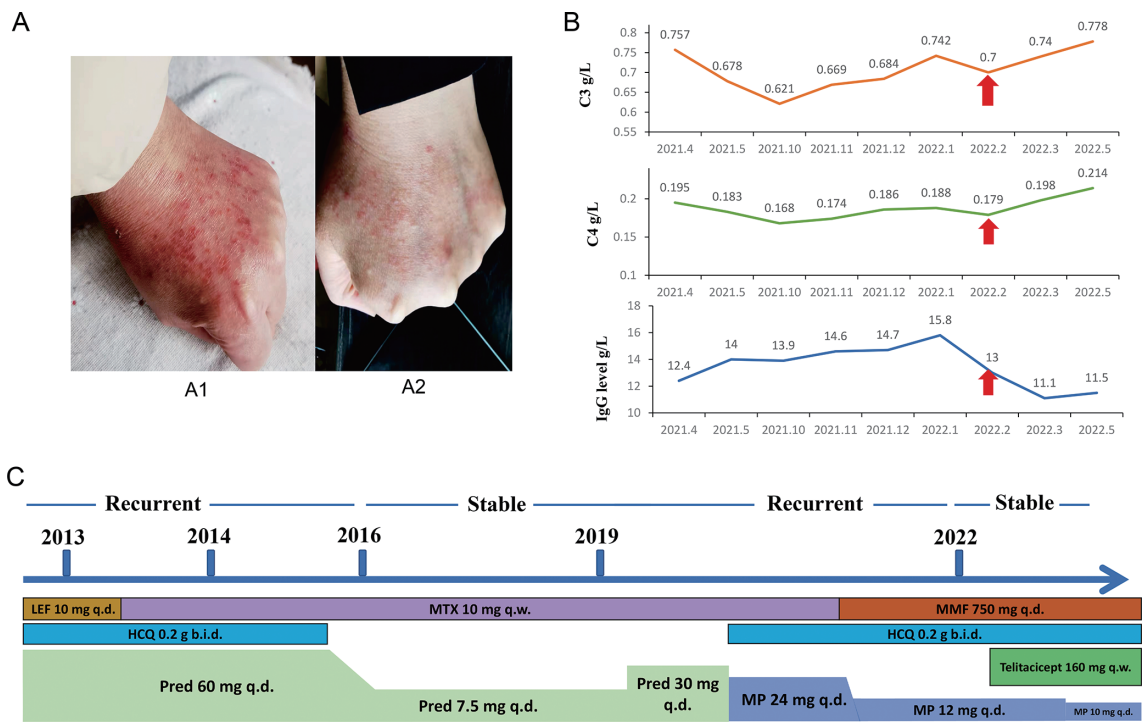

Fig. 1. Clinical profile of the patient.
(A) The photos of the hand before (A1) and 4 weeks after telitacicept (A2). (B) The changes of biomarkers; complement 3 (C3), complement 4 (C4) and IgG. Red arrows show the day of initial telitacicept. (C) The therapeutic timeline of the patient.
LEF, leflunomid; MTX, methotrexate; MMF, mycophenolate mofetil; HCQ, hydroxychloroquine sulfate; Pred, prednisone; MP, methylprednisolone.

Table 1. Review of reported studies of B-lymphocyte stimulator targeted treatments for mucocutaneous involvement of lupus.

Study, year	Population	Study design	Biological agents	No. of patients selected	Length of follow-up	Treatment protocol	Response to treatment
Vashisht et al. (2017)	SLE	Case series	belimumab	5	An average of 16 weeks	10 mg/kg weeks 0, 2, 4 and every fourth week thereafter	All 5 patients experienced significant improvement in their skin rashes during the follow up period.
Salle et al. (2020)	SLE and CLE	Case series	belimumab	16	24 weeks	10 mg/kg weeks 0, 2, 4 and every fourth week thereafter	CLASI-50 was observed in 8 patients (50%) and 3 (19%) had a complete response.
Brunner et al. (2020)	Children with SLE	RCT	belimumab	33/52	52 weeks	10 mg/kg weeks 0, 2, 4 and every fourth week thereafter	No observable difference was found in mucocutaneous BILAG organ domain improvements at Week 52.
Merrill et al. (2018)	SLE	RCT	blisibimod	236/245	52 weeks	200 mg once weekly	Rapid improvements in mucocutaneous disease activity were observed in both treatments arms at week 4 (> 10%), week 8 (> 25%), week 12 (> 40%) and beyond.
Parodis et al. (2018)	SLE	Prospective observational study	belimumab	49/62	48 weeks	10 mg/kg weeks 0, 2, 4 and every fourth week thereafter	24 patients had improved in mcSLEDAI-2K.
Zhang et al. (2018)	SLE in China, Japan and South Korea	RCT	belimumab	225/451	52 weeks	10 mg/kg weeks 0, 2, 4 and every fourth week thereafter	130 patients had improved.
Stohl et al. (2017)	SLE	RCT	belimumab	487/556	52 weeks	10mg/kg weeks 0, 2, 4 and every fourth week thereafter	Among patients with a BILAG A or B organ domain score at baseline, a significantly greater improvement was observed in mucocutaneous.
Isenberg et al. (2016)	SLE	RCT	tabalumab	689/759	52 weeks	120 mg every two weeks or 120 mg every four weeks	No differences in mucocutaneous improvement across subgroups.
Manzi et al. (2012)	SLE	Combined results from two RCT	belimumab	890	52 weeks	1 mg/kg or 10 mg/kg weeks 0, 2, 4 and every fourth week thereafter	641 patients had improved.

SLE, systemic lupus erythematosus; CLE, cutaneous lupus erythematosus; RCT, randomized controlled trial; mcSLEDAI-2K, mucocutaneous systemic lupus erythematosus disease activity Index 2000; BILAG, British Isles lupus assessment group; CLASI-50, cutaneous lupus erythematosus disease area and severity index-50.

mofetil and anti-malarials. Rapid improvement was observed as early as two weeks after initiation of therapy. To our knowledge, this is the first case that reports telitacicept for refractory cutaneous manifestations of SLE.

For cutaneous involvement of SLE, topical or systemic glucocorticoids and anti-malarials (hydroxychloroquine) is the first-line treatment. For refractory cases, methotrexate, mycophenolate mofetil and azathioprine can be added (Fanouriakis et al. 2019). BLyS targeted biologics, such as belimumab, have been reported to be efficacious in refractory cutaneous lupus. We summarized the reported studies of BLyS targeted treatments for mucocutaneous involvement of lupus (Table 1).

According to the review, belimumab has positive effects on mucocutaneous involvement of SLE. In phase III clinical trials (BLISS-52 and BLISS-76), patients with mucocutaneous features from either 10 mg/kg group or 1 mg/kg group had obvious improvement at 52 weeks (Manzi et al. 2012). In another prospective observational study, 49% of patients had improved in mucocutaneous systemic lupus erythematosus disease activity Index 2000 (mcSLE-DAI-2K) (Parodis et al. 2018). In a case series analysis involving 16 patients, cutaneous lupus erythematosus disease area and severity index-50 (CLASI-50) was observed in 8 patients (50%) and 3 (19%) had a complete response (Salle et al. 2020). Another case series study showed all of five enrolled patients experienced significant improvement in their skin rashes during an average of 16 weeks follow-up (Vashisht et al. 2017). However, in a RCT study on children with SLE, compared with placebo group, no observable difference was found in mucocutaneous British Isles lupus assessment group (BILAG) organ domain improvements at week 52 (Brunner et al. 2020).

The evidences of the efficacy of other BLyS antagonists are tenuous at best. In CHABLIS-SC1 study, the phase III clinical placebo-controlled trial of blisibimod, rapid improvements in mucocutaneous disease activity were observed in both blisibimod and placebo groups at week 4 (> 10%), week 8 (> 25%), week 12 (> 40%) and beyond (specific data were not shown) (Merrill et al. 2018). In ILLUMINATE-1 study of tabalumab, there were no differences in mucocutaneous improvement across subgroups (Isenberg et al. 2016).

As a novel recombinant TACI-Fc fusion protein, the efficacy of telitacicept for cutaneous impairment of SLE remains unclear. The phase I and IIb clinical trials of telitacicept did not provide enough data for the effects of telitacicept on mucocutaneous domain (Wu et al. 2019). In our case, the cutaneous improvement, in both face and upper extremities, was rapidly observed after initiation of therapy.

According to previous studies, BLyS and APRIL co-inhibitors are associated with increased severe toxicity. In a separate phase II/III trial of atacicept which can neutralize both BLyS and APRIL, two deaths were reported in higher dose group. Increased incidence of serious infections could be associated with rapid decline in IgG level during atacicept treatment. An approximately 30% reduction in serum IgG levels by as early as 4 weeks after initial atacicept treatment has been observed in phase I trial (Dall'Era et al. 2007). In our case, IgG level also decreased slightly, but the level was still within the normal range at 4 weeks.

In conclusion, this is the first case that reports telitacicept successfully treated a SLE patient with refractory cutaneous involvement, which provides a potential therapeutic option for recalcitrant cutaneous manifestations of SLE. Furthermore, we review reported studies of BLyS targeted treatments for mucocutaneous lupus. Further studies are warranted to assess the efficacy of BLyS antagonists for mucocutaneous involvement of SLE.

Acknowledgments

We thank the members of the National Natural Science Foundation of China (NSFC) and the Sichuan Science and Technology Program for their support. The work was supported by grant 81102274 from the National Natural Science Foundation of China (NSFC) (Hui Lin); grant 2017HH0110 supported by Sichuan Science and Technology Program (Hui Lin).

Conflict of Interest

The authors declare no conflict of interest.

References

Brunner, H.I., Abud-Mendoza, C., Viola, D.O., Calvo Penades, I., Levy, D., Anton, J., Calderon, J.E., Chasnyk, V.G., Ferrandiz, M.A., Keltsev, V., Paz Gastanaga, M.E., Shishov, M., Boteanu, A.L., Henrickson, M., Bass, D., et al. (2020) Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Ann. Rheum. Dis.*, **79**, 1340-1348.

Dall'Era, M., Chakravarty, E., Wallace, D., Genovese, M., Weisman, M., Kavanaugh, A., Kalunian, K., Dhar, P., Vincent, E., Pena-Rossi, C. & Wofsy, D. (2007) Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. *Arthritis Rheum.*, **56**, 4142-4150.

Dhillon, S. (2021) Telitacicept: first approval. *Drugs*, **81**, 1671-1675.

Durcan, L., O'Dwyer, T. & Petri, M. (2019) Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet*, **393**, 2332-2343.

Fanouriakis, A., Kostopoulou, M., Alunno, A., Aringer, M., Bajema, I., Boletis, J.N., Cervera, R., Doria, A., Gordon, C., Govoni, M., Houssiau, F., Jayne, D., Kouloumas, M., Kuhn, A., Larsen, J.L., et al. (2019) 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann. Rheum. Dis.*, **78**, 736-745.

Fernández-Nebro, A., de la Fuente, J.L., Carreno, L., Izquierdo, M.G., Tomero, E., Rua-Figueroa, I., Hernandez-Cruz, B.E., Narvaez, J., Ucar, E., Olive, A., Zea, A., Fernandez-Castro, M., Raya-Alvarez, E., Pego-Reigosa, J.M., Freire, M., et al. (2012) Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. *Lupus*, **21**, 1063-1076.

Isenberg, D.A., Petri, M., Kalunian, K., Tanaka, Y., Urowitz, M.B., Hoffman, R.W., Morgan-Cox, M., Iikuni, N., Silk, M. & Wallace, D.J. (2016) Efficacy and safety of subcutaneous

tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann. Rheum. Dis.*, **75**, 323-331.

Manzi, S., Sanchez-Guerrero, J., Merrill, J.T., Furie, R., Gladman, D., Navarra, S.V., Ginzler, E.M., D'Cruz, D.P., Doria, A., Cooper, S., Zhong, Z.J., Hough, D., Freimuth, W. & Petri, M.A.; BLISS-52 and BLISS-76 Study Groups (2012) Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann. Rheum. Dis.*, **71**, 1833-1838.

Merrill, J.T., Shanahan, W.R., Scheinberg, M., Kalunian, K.C., Wofsy, D. & Martin, R.S. (2018) Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): results from a randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.*, **77**, 883-889.

Parodis, I., Gomez, A., Frodlund, M., Jonsen, A., Zickert, A., Sjowall, C., Bengtsson, A.A. & Gunnarsson, I. (2018) Smoking reduces the efficacy of belimumab in mucocutaneous lupus. *Expert Opin. Biol. Ther.*, **18**, 911-920.

Salle, R., Chasset, F., Kottler, D., Picard-Dahan, C., Jannic, A., Mekki, N., De Risi-Pugliese, T., Monfort, J.B., Barbaud, A., Frances, C. & Descamps, V. (2020) Belimumab for refractory manifestations of cutaneous lupus: a multicenter, retrospective observational study of 16 patients. *J. Am. Acad. Dermatol.*, **83**, 1816-1819.

Stohl, W., Schwarting, A., Okada, M., Scheinberg, M., Doria, A., Hammer, A.E., Kleoudis, C., Groark, J., Bass, D., Fox, N.L., Roth, D. & Gordon, D. (2017) Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. *Arthritis Rheumatol.*, **69**, 1016-1027.

Torrente-Segarra, V., Peramiquel, L. & Bonet, M. (2021) Belimumab in subacute cutaneous lupus erythematosus. *Lupus*, **30**, 2017-2018.

Vashisht, P., Borghoff, K., O'Dell, J.R. & Hearth-Holmes, M. (2017) Belimumab for the treatment of recalcitrant cutaneous lupus. *Lupus*, **26**, 857-864.

Wu, D., Li, J., Xu, D., Wang, W., Li, L., Fang, J. & Zhang, F. (2019) A human recombinant fusion protein targeting B lymphocyte stimulator (BlyS) and a proliferation-inducing ligand (APRIL), telitacicept (RC18), in systemic lupus erythematosus (SLE): results of a phase 2b study. *Arthritis Rheumatol.*, **71** (suppl 10).

Zhang, F., Bae, S.C., Bass, D., Chu, M., Egginton, S., Gordon, D., Roth, D.A., Zheng, J. & Tanaka, Y. (2018) A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. *Ann. Rheum. Dis.*, **77**, 355-363.