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The Latest Progress in the Application of Telitacicept in Autoimmune Diseases

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Introduction: Humoral immunity plays a key role in the pathogenesis of autoimmune diseases, and B-lymphocyte activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are essential for the maintenance of B-lymphocyte reservoirs and humoral immunity. In March 2021, telitacicept, the world's first dual target three-channel biologic, was approved in China for the treatment of SLE and is currently in clinical trials exploring multiple indications for other autoimmune diseases.

Areas Covered: This article summarizes the mechanism of action, pharmacokinetics, and clinical efficacy of telitacicept for the treatment of multiple autoimmune diseases.

Expert Opinion: So far, the efficacy and safety of telitacicept in autoimmune diseases have been fully demonstrated in clinical practice. There are still many unresolved issues regarding the timing of initiation and discontinuation, still needs to be evaluated in future studies.

Keywords: biological therapy, autoimmune disease, B lymphocytes, telitacicept, immunology

Introduction

Autoimmune diseases are thought to be disorders in which the body's autoimmune system does not recognize normal cells (intracellular components) or tissues, further stimulating the body's immune response to produce autoantibodies, leading to local inflammatory reactions that eventually induce lesions or damage to tissues and organs,[1] which are associated with high morbidity and mortality,[2,3] and the treatment still faces real challenges that need to be resolved. With in-depth exploration of the pathogenesis of autoimmune diseases and the rapid development of biomedical research, telitacicept has been increasingly used in the treatment of autoimmune diseases. In this review, we will analyze the dosage, pharmacological mechanism, metabolic characteristics, and clinical application of telitacicept to help clinical physicians understand the latest research progress of telitacicept in autoimmune diseases, such as systemic lupus erythematosus (SLE), lupus nephritis (LN), IgA nephropathy, myasthenia gravis (MG) and rheumatoid arthritis (RA).

Dual BAFF/APRIL Inhibitor - Telitacicept

Mechanism of Action

BAFF, also known as B lymphocyte stimulator (BLyS), and its proliferation-inducing ligand, APRIL, have been shown to be extremely potent B-lymphocyte growth factors.[4] Studies found that BAFF binds to its receptor and plays an important role in the regulation of B lymphocyte maturation, proliferation, and activation.[5,6] The specific mechanism is mainly related to the three regulatory targets downstream of BAFF: BAFF has higher affinity for BAFF receptor (BAFFR) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) than B lymphocyte maturation antigen (B-cell maturation antigen, BCMA). BAFFR is widely distributed in all B lymphocytes except memory cells, and has been shown to maintain B lymphocyte apoptosis inhibitory factor levels

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Table 1 Summary of Clinical Trials for Different Diseases

Disease	SLE	SLE-LN	pSS	RA	IgG4-RD	NMOSD	MG	AN	IgAN	IMN	MCD
Authors	IIb clinical trial (C005SLECLLI)[16]	IIb clinical study[21]	IIb clinical study[31]	NCT03016013[35]	Dong et al[37]	Ding et al[46]	NCT04302103[51]	Ren et al[56]	ASN Annual Meeting[64]	Zhang et al[69]	Yang et al[70]
Number of patients	249	32	42	476	9	8	29	1	44	1	1
Duration	52weeks	52weeks	24weeks	24weeks	24weeks	48weeks	24weeks	4weeks	24weeks	8weeks	4weeks
Inclusion Criteria	Severely active SLE	SLE-LN	Patients with active pSS	Patients with RA with inadequate response to methotrexate	IgG4-RD patients who refused GCs	NMOSD in the acute phase	Adult patients diagnosed with systemic MG and receiving stable standard treatment	–	IgAN	–	–
Exclusion Criteria	Enrollment in another clinical trial	Enrollment in another clinical trial	Enrollment in another clinical trial	Enrollment in another clinical trial	Enrollment in another clinical trial	Enrollment in another clinical trial	MG crisis (type V)	–	Enrollment in another clinical trial	–	–
Primary end point	SRI4	Renal response rate /24h urinary protein	ESSDAI	Proportion of patients who achieved an ACR20 response	IgG4-RD response index (RI)	Time to the first recurrence after enrollment	OMG	INCAT/ anti-NF155 antibody titer	Change in urine protein 24 h from the baseline level	24h urinary protein	24h urinary protein
Overall clinical response	The SRI4 response rate was significantly higher in the telitacicept dose groups than in the placebo-combined conventional treatment group	Renal involvement was significantly improved / urinary protein level was maintained at a normal level	ESSDAIscores were significantly lower from baseline in the telitacicept 160 mg and 240 mg groups	The response rate to ACR20 increased significantly in the telitacicept group compared to the placebo group	RI was significantly reduced	Patients had no relapses or prolonged intervals between relapses at study endpoints	QMG scores were significantly lower from baseline in the telitacicept 160 mg and 240 mg groups	Anti-NF155 antibody titer stabilized at a low level of 1:10/the INCAT score decreased from 5 to 1	Patients in the telitacicept 240 mg group experienced a statistically significant 49% decrease in the mean urine protein levels 24 h rom baseline compared to the placebo group	Urinary protein level was maintained at a normal level	Urinary protein level was maintained at a normal level

Abbreviations: SLE, Systemic lupus erythematosus; LN, Lupus nephritis; pSS, Primary Sjogren's Syndrome; RA, Rheumatoid arthritis; IgG4-RD, IgG4-related disease; NMOSD, Neuromyelitis optica spectrum disorder; MG, Myasthenia gravis; AN, Autoimmune nodopathies; IgAN, IgA nephropathy; IMN, Idiopathic membranous nephropathy; MCD, Minimal change glomerulonephritis.

through non-classical and classical NF-κB pathways activated by IκB kinase 1 (IKK1) and IκB kinase 2 (IKK2); BAFFR is also essential for the survival and maturation of transitional B lymphocytes and immature B lymphocytes.[7,8] TACIs are predominantly distributed across all B lymphocytes except naïve B lymphocytes, TACI maintains plasma cell survival by affecting the NF-κB pathway; upregulation of TACI levels mediates T-cell-independent B-lymphocyte responses to antigens (for instance, marginal zone B-lymphocytes and follicular B-lymphocytes). BCMA, a cell surface receptor of the tumor necrosis superfamily required for plasma cell survival, is responsible for plasma cell differentiation and survival. The three receptors, BAFFR, TACI and BCMA, play different roles at different times in the development of B lymphocytes to ensure its differentiation and maturation (Figure 1). The fusion protein of the human IgG1 Fc segment of telitacicept binds to the specific soluble extracellular portion of TACI (Figure 2), and the TACI receptor has a strong affinity for BLyS and APRIL. Telitacicept inhibits the further development and maturation of immature B lymphocytes by blocking BLyS, inhibits the differentiation of mature B lymphocytes into plasma cells, and affects the auto-reactivity

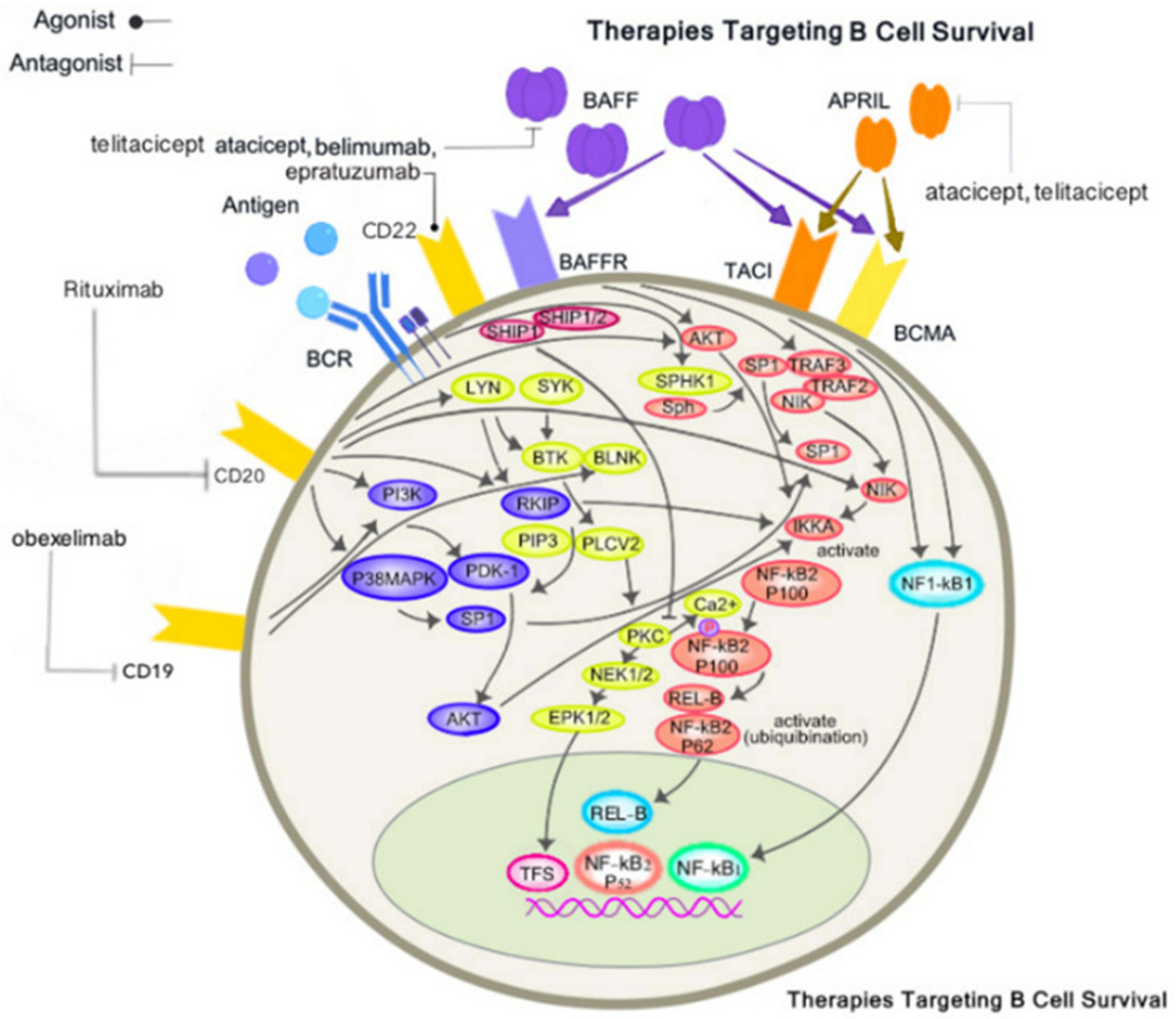

Figure 1 B-Cell Therapies That Target B-Cell Survival Inhibit Interaction of April and BAFF on B Cells.
Notes: Reproduced from Liu B, Yan, S, Yang Q, Ma Z. 贝利尤单抗治疗风湿性疾病临床研究进展 [Progress in Clinical Research on Belimumab in the Treatment of Rheumatic Diseases]. Advances in Clinical Medicine. 2024;14(1): 1673-1683.[71]

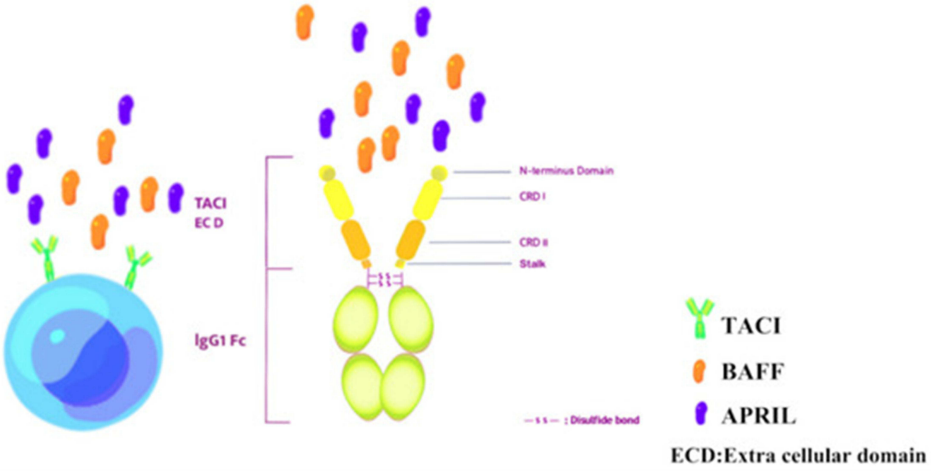

Figure 2 Mechanism of action for telitacicept.
Notes: Adapted from Cai J, Gao D, Liu D, Liu Z. Telitacicept for autoimmune nephropathy. *Front Immunol.* 2023;14:1169084.[33]

of cells through the blockade of APRIL. By blocking APRIL, it inhibits the differentiation of mature B lymphocytes into plasma cells and affects the generation of self-reactive mature B lymphocytes, plasma cells, and the switching antibody phenotypes of marginal zone B lymphocytes and follicular B lymphocytes.[9–14] The effects of telitacicept on B-lymphocytes and follicular B-lymphocytes telitacicept is less specific on BAFFR-only naïve cells and BCMA-only long-lived plasma cells.[7,15]

Pharmacokinetics

Currently, only the subcutaneous injection dose form for telitacicept is available on the market, and the recommended dose is 160 mg per injection, once a week.[16] Clinicians should fully assess the current disease activity of the patient and the safety and tolerability of the drug before applying telitacicept to decide whether to adjust the dose downward. The period of treatment for telitacicept is usually between 6 and 12 months, but the exact course should be determined by the severity of the patient's condition, response to treatment, and the physician's assessment. Use in special populations: 1) Pregnancy: Contraindicated unless it is demonstrated that the potential benefit to the fetus outweighs the risk. 2) Breastfeeding: Use with caution; it is not known whether it can be secreted into breast milk and the effects on breastfed young children and breast milk production. 3) Elderly Patient: The safety and efficacy in elderly patients over the age of 65 years have not been evaluated. 4) Pediatrics: The safety and efficacy in children and adolescents under the age of 18 years have not been determined. 5) Hepatic insufficiency: not recommended for those with hepatic impairment, regular screening for hepatitis B/c, etc. is required. 6) Renal insufficiency: no dosage adjustment is required for mild-to-moderate renal impairment, not recommended for severe renal insufficiency.[17]

Pharmacokinetic profile of a single ascending dose of telitacicept: an open Phase I population-based pharmacokinetic study has confirmed that the pharmacokinetics of telitacicept is consistent with a two-compartment target-mediated pharmacokinetic model of primary kinetic uptake.[18] In this model, the absorption and metabolism of telitacicept are similar to those of a two-compartment target-mediated drug, with the rate of absorption and transport of telitacicept being proportional to its dose. After entering the body, telitacicept is categorized into bound telitacicept, free telitacicept, and total telitacicept according to whether or not it is bound to the high-binding capacity of BLyS.[19] The binding type of telitacicept can be eliminated by internalization, and the relative magnitude of the exposure of telitacicept and its target sites in the body reflects the degree of its elimination. When the blood concentration of telitacicept in the body is less than the target amount, the clearance rate increases with increasing dose, and the drug metabolism curve shows linear characteristics, and vice versa shows nonlinear pharmacokinetic characteristics.[19,20] The metabolic profile is characterized by linear in contrast to the non-linear pharmacokinetic characteristics.

Absorption and Elimination

After the first administration of total and free serum telitacicept reach a maximum blood concentration in 24 to 48 hours (C_{max}), and after multiple injections, the blood concentration in the patient's body gradually accumulates, and then C_{max} increases.[15] After reaching the maximum concentration, blood concentration decreases exponentially and the clearance half-life ($t_{1/2}$) is 19.8 d and 11.7 d, respectively, for total and free serum telitacicept, and Cmax trends and the drug-time curve (*AUC*) are similar.[15,19]

Pharmacokinetics of Multiple Doses of Telitacicept in Patients With SLE

The mean peak serum concentrations of free telitacicept measured in healthy subjects and SLE patients who received weekly subcutaneous injections of telitacicept (160 mg) in combination with standard therapy are 4.72 μg/mL and 4.5 ug/mL, respectively.[15] After the first injection of telitacicept in patients with SLE, the mean concentration at steady state reach approximately 2 μg/mL and the apparent clearance rate (CL/F) is 208 mL/h. The formation and elimination of conjugated telitacicept is slow, and the Cmax could only be reached after giving telitacicept for approximately 17–63 d. In addition, the phenomenon of accumulation of blood concentration in vivo is observed, and it could be gradually eliminated after 7 weeks, with a $t_{1/2}$ of 19.4 d and its $t_{1/2}$ increases with increasing telitacicept dosage.[15] Studies have shown that after subcutaneous injection of 180 mg of telitacicept per week for 4 weeks, the bound telitacicept measured on the 84th day was still greater than 50% of C_{max}.[15] The long-lasting in vivo effect and stable blood concentration of telitacicept also remind clinicians that special attention should be paid to the dosage and accumulation effects of telitacicept.

Drug Interactions

No formal drug–drug interaction studies have been conducted, and in the Phase IIb clinical trial of telitacicept in patients with SLE:[16] telitacicept was administered in combination with standardized therapeutic agents, including glucocorticoids (GCs), antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants or immunomodulators (including azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, leflunomide, tacrolimus, cyclosporine), and angiotensin-converting enzyme inhibitors and/or angiotensin receptor antagonists when accompanied by elevated blood pressure or renal involvement, and there is no evidence that these drugs significantly affect the pharmacokinetics of telitacicept.

Clinical Applications

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease characterized mainly by the production of a large number of autoantibodies in the body.[20,21] Currently, the treatment of SLE includes mainly GCs and immunosuppressants. With further research on the pathogenesis of SLE, BLyS activation has been found to be an important factor in the development of SLE, and abnormal activation of B-lymphocytes is involved in almost all processes of SLE. The efficacy of BLyS/APRIL-targeted B-lymphocyte therapy is similar or even superior to that of conventional therapies, with fewer adverse effects and a faster onset of action.[21] Recent studies have found that telitacicept is more effective in slowing the progression of SLE.

Telitacicept is commonly used in the clinic as a treatment option in addition to conventional therapy (GCs combined with immunosuppressants) in adult patients with SLE who still have autoantibody positivity, low complement, and high disease activity based on conventional therapy with a systemic Lupus Erythematosus Disease Activity Index (SEIENA-SLEDAI) score of ≥8. Neuropsychiatric lupus, acquired immunodeficiency syndrome (AIDS), active infections, tuberculosis, hepatitis B, hepatitis C, patients with a history of cell transplantation are contraindications.[17] Recently, a single-center, randomized, single-blind, placebo-controlled phase I exploratory clinical trial evaluated the safety and efficacy of multiple doses of telitacicept for the first time. The results showed that there was no significant difference in the SLEDAI-2K scores between the two groups; however, peripheral blood lymphocyte counts (CD19+B lymphocytes and IgD+B lymphocytes) and serum immunoglobulin levels were lower in patients with SLE in the telitacicept group.[14]

Preliminary evaluation of the safety and the efficacy-dose relationship was assessed for the treatment of patients with severely active SLE in a 52-week multicenter, randomized, double-blind, placebo-parallel controlled phase IIb clinical

trial (C005SLECLLI).[16] A total of 249 patients with SLE with high disease activity were enrolled. This study used the SLE Response Index (SRI4) as the primary endpoint of the evaluation criteria. The results showed that the SRI4 response rate at week 48 was significantly higher in the telitacicept groups than in the placebo-combined conventional treatment group; the risk of serious recurrence at week 52 was reduced by 55.8% in the telitacicept 80mg group (HR = 0.442), by 55.5% in the 160mg group (HR = 0.445) at week 52, and by 72.0% in the telitacicept 240mg group (HR = 0.280). This trial concludes that telitacicept reduces disease activity and prevents flares in SLE compared to placebo combined with conventional therapy.

In the dose range of 80 mg, 160 mg, and 240 mg, the efficacy of telitacicept increased with increasing, showing a clear quantitative effect relationship: the incidence of adverse reactions of telitacicept in the 80 mg group was close to that of the 160 mg group, while the 240 mg group had a slightly higher incidence; combining efficacy and safety, it is recommended to use telitacicept at a dose of 160 mg.

Similar conclusions were found in a 52-week, multicenter, dynamic, randomized, double-blind, placebo-controlled Phase III clinical study in China, and confirmed the safety and efficacy of subcutaneous injection of telitacicept (160 mg once/week) in combination with conventional therapy in patients with highly active adult SLE. A total of 335 patients with SLE were enrolled in the study, andtelitacicept (160 mg) was subcutaneously injected once a week for 52 doses at the time of the study and visits were made every 4 weeks during the treatment period. The GCs were reduced in subjects who had at least 4 weeks of improvement in their SLE disease, as judged by the investigator, and the GC were gradually reduced in the study. The primary endpoint was the SRI4 response rate at week 52. At week 52, Results showed a significantly higher response rate in the telitacicept 160 mg group than in the placebo group (82.6% vs 38.1%, $P < 0.001$); and subjects who did not worsen (compared to baseline, PGA score <0.3 points) were significantly higher than those in the placebo group (97.6% vs 91.1%, $P = 0.009$); Overall adverse events were similar between the two groups (91.6% vs 84.5%), suggesting a favorable safety profile for telitacicept. During the trial period, the number of severe relapses was significantly lower in the telitacicept group than in the placebo group (10% vs 60%, $P < 0.001$); This study demonstrated a significant role in decreasing disease activity in SLE patients and in delaying the time to recurrence, the telitacicept group was more effective and the incidence of serious adverse events was lower than in the placebo group.[22]

A recent retrospective, observational real-world study evaluated the efficacy and safety of telitacicept for the treatment of SLE,[23] enrolling a total of 20 patients with SLE treated with telitacicept for ≥4 weeks, with the primary treatment endpoint being the SRI-4 response rate, who received weekly subcutaneous injections of telitacicept 160 mg on top of the standard treatment regimen for the duration of the study. The study results showed an overall SRI-4 response rate of 80% for telitacicept, and SLEDAI scores and the remaining indicators representing disease activity were significantly lower. GCs dose was significantly reduced in SLE patients under telitacicept treatment. The proportion of patients who did not require immunosuppressive therapy increased from 15% to 43% at the end of treatment. This real-world study provided good evidence for the results of the clinical trial of telitacicept, demonstrating that telitacicept is effective and safe in the treatment of SLE.

The results of the above clinical studies on the treatment of SLE with telitacicept showed superior clinical efficacy and a favorable safety profile, with clinical improvements accompanied by reductions in steroid dose, immunoglobulin levels, total B-cell subsets, and initial B-cell subsets. Recently, the Chinese Expert Consensus on the Use of Biologics in SLE (2024 Edition) suggests that when SLE patients do not respond to hydroxychloroquine (alone or in combination with GCs), biologics (eg, telitacicept) can be added without trying immunosuppressants. The early use of biologics (telitacicept) is expected to provide additional benefits to SLE patients.

Lupus Nephritis

Lupus nephritis (LN) is a common and serious complications of SLE, with a prevalence of more than 90%.[24,25] A recent study showed reduced mortality and decreased serum IgM, IgG, and anti-dsDNA in APRIL-deficient LN. Another study in mice with rapidly progressive LN showed that inhibition of BLyS expression prevented and treated LN, significantly reduced proteinuria levels, and prolonged survival.[26] Chen et al[27] reported a case of refractory proliferative LN with arthralgia and proteinuria as the first clinical manifestations, after the treatment with GCs, hydroxychloroquine,

mycophenolate mofetil and telitacicept (160 mg once weekly) treatment, and during the 19 months of follow-up, the patient experienced a sustained decrease in proteinuria levels, good control of creatinine levels and blood pressure, and no end-stage renal disease.

A self-controlled retrospective study evaluated the efficacy and safety of telitacicept in the treatment of refractory SLE (cSLE) in children. After 5 to 26 weeks of telitacicept intervention (80 mg or 160 mg subcutaneously weekly), 10 of 15 patients with refractory cSLE achieved an SRI4 response. The patient's GCs dosage and urinary protein decreased to different degrees, and renal function improved.[28]

The results of a Phase IIb clinical study showed that the renal response rate was significantly higher in the telitacicept (80 mg, 160 mg, 240 mg subcutaneous injection, once/week) group than in the placebo group from week 4, and that renal involvement was significantly improved at week 52. Among them, the improvement rate of the telitacicept 240 mg group was significant compared to the placebo group ($P < 0.05$), the 24 hour urinary protein was reduced at the beginning of week 4, and the difference in its reduction value was substantial compared to that of the placebo group. At the endpoint of the study, urinary protein continued to decrease in all telitacicept dose groups, with urinary protein decreasing to approximately 0.5 g/24 h in the 240 mg group.[21] In a Phase III clinical study,[22] the results showed a statistically significant difference between the telitacicept 160 or 240 mg group compared to placebo, with a more pronounced reduction in 24-h urine protein levels in the telitacicept 160 mg group. Two studies demonstrated that telitacicept increased renal response rate and improved renal function in patients with SLE-LN. In a real-world study, 14 of 19 patients with LN (baseline 24-h proteinuria >0.5 g/d) had a significant reduction in median 24-h urine protein, with 7 patients turning negative. Fifteen hypoalbuminemic patients with LN all had improved albumin with treatment; Three patients with comorbid renal impairment had significantly higher eGFR. The therapeutic efficacy and safety of telitacicept in patients with LN are significant, and it provides a new option for the treatment of LN.

Primary Sjogren's Syndrome

Primary Sjogren's Syndrome (pSS) is an autoimmune disease mediated by a combination of immune cells and multiple inflammatory factors.[29] pSS is a highly B-lymphocyte-active disease, with sustained activation of autoreactive B-lymphocytes throughout the course of pSS.[30] Newer studies have found that telitacicept is highly effective in the treatment of pSS. A new 24-week, multicenter, randomized, double-blind, placebo-controlled Phase II clinical trial was the first to initially investigate the efficacy and safety of telitacicept in the long-term treatment of patients with pSS.[31] A total of 42 pSS patients were enrolled, and the telitacicept 160 mg and 240 mg group were administered once a week for a total of 24 doses, with visits every 4 weeks during the double-blind treatment period, which also allowed the use of NSAIDs, hydroxychloroquine, and artificial tears if the condition required them. The primary study endpoint was the amount of change from baseline in the ESSDAI score at week 24. The results showed that at week 24, the change values from baseline in the ESSDAI scores in the telitacicept 160 mg, 240 mg and placebo groups were −4.0, −3.1, and −0.2 points, respectively, and SS disease activity index (ESSDAI) scores were significantly lower ($P < 0.05$); the telitacicept SS Patient Reported Index (ESSPRI) scores decreased to some extent from baseline at week 12 and 24, but the differences between the groups were not statistically significant due to the small sample sizes of the groups. Also, salivary function and lacrimal function were improved to varying degrees in the patients in the telitacicept group compared to the placebo group. Compared to the placebo group in the Schirmer I test of 5 min at week 24; The scales corresponding to the leading edge of the infiltrated portion of the filter paper strip with statistically significant longer between the 240 mg group and the placebo group ($P = 0.019$), the salivary flow rate of the 160 mg and 240 mg groups increased compared to baseline at the 12th and 24th week after telitacicept treatment. At week 24, the difference between the groups in the rate of change from baseline in the C4 level in the 160 and 240 mg groups, the mean change rate (%) in IgG, IgA and IgM levels from baseline in the 160 and 240 mg groups and the difference in the rate of change from baseline in CD19+ B lymphocyte counts in the telitacicept 160 and 240 mg group were statistically significant compared to the placebo group. Overall adverse events were the same in the telitacicept group and in the placebo group (92.9% vs 92.9%), and there were no serious adverse events or deaths in any of the telitacicept groups. Hematological and urinalysis changes were similar between subjects in the telitacicept and placebo groups before and after the intervention in this study, and there was no increased risk of hepatic or renal impairment during the 24 weeks of telitacicept intervention. At

week 24, two patients (14.3%) in the telitacicept 240 mg group turned negative for anti-SSA antibodies. This study preliminarily confirmed the effectiveness of telitacicept in pSS, providing more drug options for patients with pSS. However, there are many deficiencies in the treatment endpoints selected in this study, the evaluation system involving the salivary and lacrimal glands is not sufficiently sensitive, and the enrollment of patients with advanced disease has irreversible gland function, which does not better reflect the efficacy of the study drug, etc. In the future, there is still a need for a more sensitive evaluation system to assess the safety and efficacy of telitacicept in the treatment of pSS.

A phase III multicenter, randomized, double-blind, placebo-controlled clinical trial is currently underway in China,[32] which aims to evaluate the efficacy and safety of telitacicept in patients with active pSS (NCT05673993). But the results have not been blinded at this time.

There are currently no biologics approved globally for the treatment of Sjogren's syndrome, and telitacicept is expected to fill this gap and bring new treatment options to patients.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease with synovitis, articular cartilage, and bone destruction as the main clinical manifestations. Studies have shown that B lymphocytes and plasma cells can be detected on the synovial membrane of RA patients; Furthermore, RA patients have obvious autoantibody responses, and high-affinity IgG and IgA antibodies against citrullinated, carbamoylated, and acetylated proteins in the body. Several studies also have shown that the removal of B cells significantly reduces signs and symptoms of RA, suggesting that B lymphocytes play an important role in the pathogenesis of RA. Telitacicept, as a dual inhibitor of BLys/APRIL, has shown its value as an effective treatment for RA.[33] Non-clinical studies showed that telitacicept is as effective as methotrexate on collagen-induced arthritis (CIA) mice by ameliorating joint and spleen pathology, regulating T and B lymphocytes function. And administration of telitacicept significantly reduced the arthritis global assessment and swollen joint count (SJC) and ameliorated histopathological manifestations of rat adjuvant arthritis.[34]

A 24-week, large-sample, randomized, double-blind, placebo-controlled group phase III clinical trial has recently been completed in a target population of patients with RA with inadequate response to methotrexate response to assess the efficacy and safety of telitacicept in the treatment of RA (NCT03016013).[35] A total of 476 patients with RA were enrolled in the study and lasted for 24 weeks, with an open-label follow-up period after 25 weeks to 48 weeks. During the study period: patients in the telitacicept group were treated once a week; after 24 weeks of observation, patients in the placebo group were switched to 160 mg of telitacicept once a week to continue treatment for 24 weeks. The primary efficacy endpoint of the study was the proportion of patients who achieved an ACR20 response at week 24; Secondary study endpoints included ACR50 and ACR70 response rates, individual components of the ACR response, DAS28-ESR, and radiographic joint damage, measured by modified total sharp score (mTSS) at week 24. The results indicated that at week 24, the response rate to ACR20 increased significantly in the telitacicept group compared to the placebo group (60.0% vs 26.9%, $P < 0.001$). At week 24, the telitacicept group had a significantly higher ACR50 response rate than the placebo group (21.4% vs 5.9%, $P < 0.001$), a lower DAS28-ESR from baseline and significantly better components of the ACR response criteria than the placebo group. In addition, the proportion of RA patients with no significant radiologic progression at week 24 ($\Delta mTSS \leq 0$) was significantly higher in the telitacicept group than in the placebo group (90.20% vs66.40%, $P < 0.001$). The progression of joint damage (mTSS, joint space narrowing score and erosion score) was significantly reduced at week 24 in RA patients in the telitacicept group compared to baseline. The telitacicept group was similar to the placebo group in terms of treatment-related adverse events (TEAEs), serious adverse events (SAE), TEAEs that led to discontinuation of the study, and incidence of infections, with no deaths observed during the study period. The results of this phase III study indicate that telitacicept demonstrated favorable results in patients with moderate-to-severe RA with inadequate response to methotrexate and was well tolerated in patients with RA who had failed prior therapy. Recently, the Center for Drug Evaluation (CDE) of the State Drug Administration has accepted the application of RA as a new clinical indication for telitacicept (https://www.nmpa.gov.cn/zwfw/sdxx/sdxxyp/yppjfb/20240719151602155.html). This provides strong support for the use of telitacicept as a new treatment option for RA.

IgG4-Related Disease

IgG4-related disease (IgG4-RD) is a group of diseases characterized by chronic inflammation mediated by the immune system accompanied by fibrosis with IgG4+ plasma cell infiltration as the main pathological manifestation.[36] Dong et al[37] reported for the first time a case of IgG4-RD that was effective in response to treatment with telitacicept. To further investigate the safety and efficacy of telitacicept in IgG4-RD, a single-center prospective single-arm small sample clinical trial with a duration of 24 weeks was conducted. The results showed that the IgG4-RD response index (RI), serum IgM, IgE, and CD19+, CD20 and plasmacytoma cell levels were significantly reduced. Currently, treatment options for IgG4-RD patients are limited, and for patients who refuse hormone treatment, especially those with high levels of ESR, IgG4, and plasma cells, telitacicept treatment has a potential therapeutic effect in reducing the size of the lesion, relieving symptoms, and improving laboratory markers. Of course, future studies with larger sample sizes are needed to evaluate the safety and efficacy of telitacicept in the treatment of IgG4-RD and to further define the optimal potency ratio and duration of dosing.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease characterized by immune-mediated involvement of the central nervous system (CNS), the main causative autoantibody being astrocyte aquaporin-4 (AQP4).[38,39] It has been found to play an important role in the pathogenesis of NMOSD, and therapeutic means targeting abnormal proliferation of B lymphocytes have been gradually emphasized. And there is an overexpression of BLyS and APRIL in NMOSD and correlates with disease activity and severity.[40] Experimental autoimmune encephalomyelitis (EAE) is an internationally recognized animal model for the study of multiple sclerosis (MS), and studies have confirmed the safety and effectiveness of telitacicept intervention in EAE.[41–44] The study confirmed the safety and effectiveness of telitacicept in intervening in EAE. Therefore, telitacicept may be a potential therapeutic agent for NMOSD.[45]

Recently, a small-sample, single-center, single-arm, open clinical study of plasma exchange in combination with telitacicept for the treatment of recurrent NMOSDs over a 48-week period was showed that patients in the telitacicept-treated group had longer intervals and fewer recurrences than those in the control group ($P < 0.001$). Patients had a 0.83-point reduction in the Evaluation of Neurological Status Scale (EDSS) score, and B-lymphocyte counts peaked at 12 weeks and then declined, BLyS and APRIL levels gradually declined during the course of treatment; serum IgG and IgA both declined at 48 weeks of treatment.[46,47] In this study, the researchers found that after plasma exchange removes pathogenic antibodies from NMOSD patients, the use of telitacicept inhibits autoimmune responses and antibody production in NMOSD patients, thereby prolonging the relapse interval and reducing EDSS scores with a favorable safety profile. This exploratory study lays an academic foundation for new treatment options for NMOSD patients. However, large-sample, multicenter, randomized controlled studies are still needed to further clarify the safety and efficacy of telitacicept in the treatment of NMOSD.

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disease with autoantibody-mediated impairment of acquired nerve-muscle junction transmission.[48] Autoantibodies produced by B-lymphocytes or plasma cells are closely related to the pathogenesis of MG, with acetylcholine receptor (AChR) antibodies being a key mediator. Recent studies have shown that serum BAFF levels are upregulated in patients with anti-AChR antibody-positive MG, including thymoma-associated MG, and correlate with itstiters[49] and APRIL levels were also elevated.[50] Therefore, targeting BLyS/APRIL has become a new idea for the treatment of patients with MG. In order to preliminarily evaluate the safety and efficacy of telitacicept in MG patients, a 24-week phase II multicenter, randomized, open clinical study (NCT04302103) was completed in China.[51] The study results showed that at week 24, the mean reduction in quantitative myasthenia gravis score (QMG) in the group of telitacicept was significant decrease. Secondary endpoints were telitacicept group experienced a significant reduction in clinical absolute scores of MG compared to baseline, which persisted until week 24. And telitacicept significantly improved the condition of patients, demonstrating good efficacy and safety. Zhang et al[52] reported two patients with refractory generalized MG with generalized weakness as the first manifestation. Both

were effectively treated with telitacicept, with significant improvement in symptoms and a significant decrease in OMG scores. Single-targeted biologics may face certain limitations in the treatment of MG.[53] BLyS and APRIL together play an important regulatory role on B cells and plasma cells, and are key warrants for the treatment of autoimmune diseases, including MG. The dual-targeted biologic agent, telitacicept, showed clinically meaningful efficacy and safety in its phase II clinical study for the treatment of MG, and is expected to provide a new modality for the treatment of MG.

Autoimmune Nodopathies

Autoimmune nodopathies (AN) are a class of peripheral motor sensory neuropathies mediated by antibodies to Langfell's node-paranodal cell adhesion molecules (CNTN1, NF155, Caspr1) and nerve fasciculin antibodies related to nerve fasciculin (NF140/186).[54] Currently, some studies have shown that telitacicept can reduce the chronic inflammation associated with NF155+ AN.[55] Ren et al[56] reported a case of a female patient with NF155+AN who after telitacicept (160 mg) weekly subcutaneous injections, the patient's serum anti-NF155 antibody titer stabilized at a low level of 1:10, while clinical symptoms gradually improved, the Inflammatory Neuropathy Causes and Treatments (INCAT) score was decreased, reflecting the positive therapeutic effect of telitacicept. Previous studies have shown that NF155+AN patients respond poorly to immunoglobulin or GCs therapy, whereas they usually respond well to rituximab therapy.[57] However, in the present case, PE combined with rituximab did not improve patient clinical symptoms, and patient's anti-NF155+ antibody titer increased significantly. This may be related to the fact that the patient's CD19+ cell count decreased significantly after rituximab treatment, while the proportion of plasmablasts to B lymphocytes was abnormally high at 77.3%. These plasmablasts act as a type of antibody-secreting cell (ASC) that can continue to differentiate into short-lived and long-lived plasma cells, thus continuing to secrete large amounts of antibodies over a longer period of time.[56,57] This also suggests the heterogeneity of the treatment of patients with NF155+AN in the clinic and the need for active exploration of alternative therapeutic strategies in the clinic.

IgA Nephropathy

IgA nephropathy (IgAN) is a chronic inflammatory autoimmune disease characterized by proliferation of glomerular mesangial membranes and IgA deposition within the mesangium.[58] The current pathogenesis of IgAN is complex, and the doctrine of multiple hits is widely recognized in the academic community. Multiple studies have shown that IgA were correlated with BAFF and APRIL expression levels, which also can influence the progression of IgAN disease.[59–63] Therefore targeting BAFF/APRIL may become a new therapeutic strategy for IgAN.

Telitacicept has a favorable track record in the treatment of IgAN. At the 2021 ASN Annual Meeting, the results of a randomized, double-blind, placebo-controlled Phase II clinical trial of 24 weeks that initially evaluated the safety and efficacy of telitacicept in IgAN were reported.[64] The results found that the patients in the telitacicept 160/240 mg group experienced a statistically significant 25/49% decrease in the mean urine protein levels 24 h rom baseline compared to the placebo group; and the eGFR remained stable throughout the dosing period in all groups. At week 24, the levels of Gd-IgA1 and IgA immune complexes were significantly reduced compared to baseline. Telitacicept reduced proteinuria in high-risk IgAN patients, may reduce the risk of disease progression in IgAN patients, and could be a new treatment option for IgAN in the future.

Idiopathic Membranous Nephropathy

Idiopathic membranous nephropathy (IMN) is often manifested as podocyte apoptosis, necrosis, and absence, and the clinical manifestation is large proteinuria. Recent studies have shown that serologic BAFF levels in patients with IMN are higher than those of healthy controls, while APRIL levels are comparable to those of healthy controls. Furthermore, BAFF levels were higher in patients with relapsed IMN than in healthy controls, while APRIL levels were higher in patients with unremitting IMN. BAFF and APRIL expression levels, like those of other autoimmune diseases, correlate with the renal prognosis.[65] TIn recent years, rituximab has emerged as a classic treatment option for refractory IMN, with evidence that rituximab treatment maintains and relieves proteinuria for up to 24 months compared to cyclosporine.[66] Ruggenenti et al[67] found that approximately 30% of patients with IMN did not respond well to rituximab, which may be related to the fact that long-lived memory plasma cells do not express CD20. By blocking BLyS and inhibiting the further

development and maturation of immature B lymphocytes, telitacicept helps control disease progression; By blocking APRIL, it inhibits the differentiation of mature B lymphocytes to plasma cells and influences the secretion of autoantibodies by autoreactive plasma cells, which can better control disease activity and realize multistage inhibition of B lymphocyte maturation and differentiation. Meanwhile, due to the presence of the TACI receptor on the cell membrane, telitacicept can also inhibit the activity of T lymphocytes.[68] Zhang et al[69] reported for the first time a case of refractory membranous nephropathy, proteinuria completely disappeared after administration of GC combined with telitacicept, which is a good example for the treatment of refractory Idiopathic membranous nephropathy (IMN) by telitacicept. In the future, large-sample multicenter clinical trials are needed to evaluate whether B-lymphocyte multi-targeting drugs are superior to single-targeting drugs. The safety and efficacy of telitacicept in IMN patients also deserve further attention.

Minimal-Change Glomerulonephritis

Minimal change glomerulonephritis (MCD) is a common type of idiopathic nephrotic syndrome, prevalent in young males, and is often characterized by massive proteinuria, edema, and hypertension. A recent study showed that telitacicept is highly effective in MCD, and Yang et al reported a case of MCD with bilateral lower extremity edema and large amounts of proteinuria as the first manifestation of MCD, which telitacicept combined with GCs treatment was initiated for 4 weeks, and the patient's urinary protein returned to normal level, providing new evidence for the treatment of MCD with telitacicept.[70] Summary of Clinical Trials for Different Diseases show on the Table 1.

Safety and Adverse Reactions

In general, the efficacy and safety profile of telitacicept is favorable compared to other comparable B-lymphocyte-targeted drugs. It has been suggested that telitacicept reduces serum globulin levels and peripheral blood lymphoid counts (CD19+ B lymphocytes and IgD+ B lymphocytes) in patients with SLE, and that infections are the most common adverse effect.[14] The results of a study in 28 Chinese patients with RA showed that telitacicept at subcutaneous doses of up to 540 mg had a favorable safety and tolerability profile, with mild to moderate infections and transient injection site reactions more common than in patients receiving placebo.[13] Studies have shown that dual target APRIL/BlyS therapy has a favorable safety and tolerability profile in healthy populations.[72] However, there have been several cases of progressive multifocal leukoencephalopathy described in patients treated with belimumab.[73–75] The current clinical studies of telitacicept have shown that it is safe and well tolerated. Although no adverse events related to progressive multifocal leukoencephalopathy (PML) have been reported in the current clinical study of telitacicept, it is still recommended that clinicians take full into account the neurological and other clinical manifestations of patients when using telitacicept, and should draw attention to discontinue immunosuppressive treatment, in a timely manner when there are clinical signs of PML.

Discussion

B lymphocytes are pivotal in the development of autoimmune diseases, as the abnormal proliferation and impaired clearance of B cells lead to the activation of autoantigens, which triggers the secretion of pathogenic autoantibodies. For autoimmune disorders marked by significantly increased levels of BLyS and APRIL in the serum, such as SLE, LN, pSS, RA, and IgAN, targeting the production of BLyS and APRIL in the body using telitacicept emerges as a logical therapeutic approach. Evidence from ongoing clinical trials and real-world studies supports the safety and efficacy of telitacicept treatment, particularly for patients with mild-to-moderate SLE. It is crucial, however, to acknowledge that most of these studies are of relatively short duration, have a small cohort of participants, and have a high rate of compliance, and there is a significant potential for publication bias in the reporting of observational studies. Additionally, the beneficial effects of telitacicept are often highlighted in post-hoc analyses.

Currently, there is a notable scarcity of data regarding the safety and efficacy of telitacicept in managing severe SLE cases, especially those with significant involvement of critical organs, such as the heart, lungs, liver, kidneys, and central nervous system. Consequently, recommending it as a standard treatment option in these scenarios would be premature.

Furthermore, telitacicept's safety and efficacy have not been thoroughly evaluated in specific patient demographics, including pregnant women, rendering its use in such cases not yet justifiable based on existing evidence.

Telitacicept is frequently associated with enhancements in patients' quality of life, likely due to its substantial role in reducing the required dosage of GCs. As such, for individuals who have been subjected to long-term, high-dose GCs therapy or those who are unable to tolerate these medications, telitacicept presents a viable alternative treatment option. By diminishing disease activity and averting the recurrence of autoimmune conditions, telitacicept has the potential to mitigate organ damage and favorably influence the course and prognosis of the disease. Nonetheless, this assertion warrants further substantiation through broader, multicenter, randomized controlled trials.

A significant limitation of telitacicept therapy is the necessity for it to be administered alongside continuous standard treatments as a complementary therapy. The safety of reducing or discontinuing GCs or lowering the dosage of antimalarial drugs and immunosuppressants during telitacicept therapy remains uncertain and is yet to be methodically investigated.

Future studies are imperative to determine the optimal initiation time for telitacicept therapy, which might be particularly beneficial for specific patient groups, such as those at an elevated risk of disease flare-ups or facing higher drug toxicity risks. The identification of novel biomarkers within the spectrum of autoantibodies and complement levels could facilitate the selection of individuals most likely to benefit from telitacicept therapy. Given the disappointing outcomes of other B-cell-targeting therapies in autoimmune disease treatment, an increased emphasis on accurately identifying patients who stand to benefit most from such treatments is necessary. This entails making informed decisions regarding treatment timing, assessing disease severity, and monitoring early biomarker responses.

Conclusions

Telitacicept inhibits the overexpression ofBLyS and APRIL, which plays a therapeutic role while preserving autoimmunity. To date, it has been effective in clinical trials of SLE, LN, pSS, RA, IgG4-RD, NMOSD, MG, AN, IgAN, IMN, and MCD, demonstrating a broad promise for the treatment of B-cell related diseases. In the future, we look forward to the publication of more clinical data on the treatment of autoimmune diseases with telitacicept for the benefit of the patients concerned.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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