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CCC: 0377-8282/2001

Abetimus Sodium

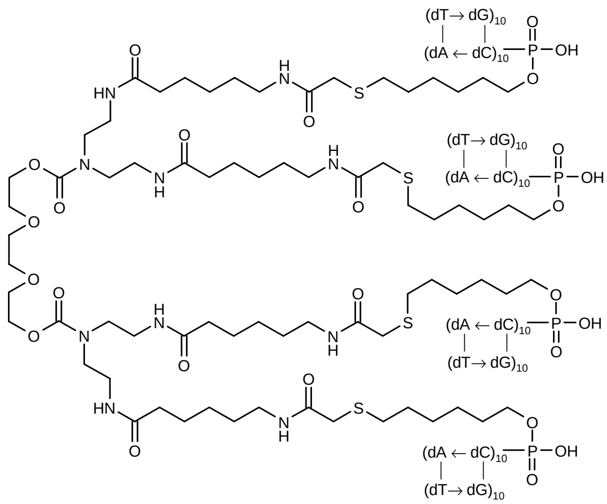
Prop INN; USAN

Treatment of Systemic Lupus Erythematosus

LJP-394
Rentol™

DNA d(C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A), 5'-ester with 1,2-ethanediylbis(oxy-2,1-ethanediyl)bis[2-(21,21-dihydroxy-21-oxido-4,11-dioxo-20-oxa-13-thia-3,10-diaza-21-phosphaheneicos-1-yl)-23,23-dihydroxy-23-oxido-6,13-dioxo-22-oxa-15-thia-2,5,12-triaza-23-phosphatricosanoate] (4:1), complex with DNA d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) (1:1), hexapentacontahectasodium salt

Deoxyribonucleic acid d(C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A), 5'-ester with 1,2-ethanediylbis(oxy-2,1-ethanediyl)bis[2-(21,21-dihydroxy-4,11-dioxo-20-oxa-13-thia-3,10-diaza-21-phosphaeneicos-1-yl)-23,23-dihydroxy-6,13-dioxo-22-oxa-15-thia-2,5,12-triaza-23-phosphatricosanoate] (4:1), *P*,*P*',23,23'-tetraoxide, complex with deoxyribonucleic acid d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) (1:1), hexapentacontahectasodium salt



$C_{1632}H_{1944}N_{610}Na_{156}O_{970}P_{156}S_4$

CAS: 169147-32-4
CAS: 167362-48-3 (as free acid)

EN: 217652

Description

Abetimus is a tetravalent conjugate comprised of four double-stranded 20-mer oligonucleotides consisting of alternating deoxycytidine-deoxyadenosie, $(CA)_{10}$, and its complementary thymidine-deoxyguanosine, $(TG)_{10}$, attached to a fully defined nonpolymeric platform consisting of triethylene glycol modified with alkyl-amide-branching groups (1).

Introduction

Systemic lupus erythematosus (SLE) is a chronic, life-threatening, inflammatory autoimmune disease which affects 40-50 individuals for every 100,000. Of those individuals suffering from the disorder, 90% are females who predominantly develop the disease during childbearing years. About half of all patients with SLE will develop organ-threatening diseases such as heart, lung and kidney disease, autoimmune hemolytic anemia and CNS inflammation. Serious kidney damage or lupus nephritis occurs in about 50% of all patients with organ-threatening SLE. It is characterized by periods of remission and life-threatening kidney inflammation known as flares. The other 50% of all SLE patients will have non-organ-threatening disease showing symptoms including fever, arthralgia, myalgia, synovitis, serositis, fatigue, rash, weight loss and/or swollen glands (2, 3).

The immune dysregulation seen with SLE is characterized by polyclonal B cell activation and the production of autoreactive antibodies directed against nuclear antigens and other self-antigens (4). It is these autoantibodies which cause organ injury via direct antigen recognition on target cells. Autoimmune complexes made up of the autoreactive antibodies and antigens are formed and can bind complement. They eventually cause organ damage through activation of humoral and cellular mediators of inflammatory responses such as activation of complement, fibrin deposition and polymorphonuclear and mononuclear cell recruitment and activation. Moreover, these autoimmune complexes can directly bind to highly charged nuclear histone antigens and anti-DNA antibodies. Thus, a serological marker of SLE is the antinuclear antibody which has been detected in about 98% of all patients. At least 50% of SLE patients with

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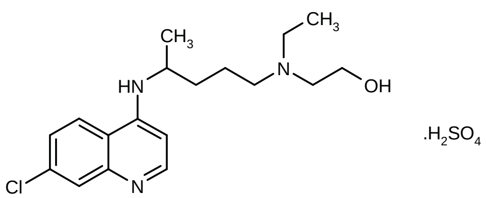
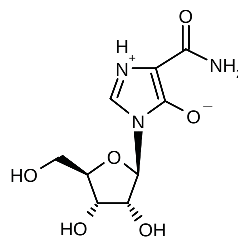
Table I: Compounds available and under development for the treatment of systemic lupus erythematosus (Prous Science Integrity database).

Drug Name	Company	Mechanism of Action	Status
1. Hydroxychloroquine sulfate (*Plaquenil*)	Sanofi-Synthélabo		Launched-1956
2. Mizoribine (*Bredinin*)	Asahi Chem.	Immunosuppressant	Launched-1984
3. Dehydroepiandrosterone	Genelabs/Watson	Immunosuppressant	Preregistered
4. Abetimus sodium	La Jolla Pharm.	Tetrakis-oligonucleotide conjugate that removes double-stranded DNA autoantibodies	Phase III
5. Tacrolimus (*Prograf*)	Fujisawa	Macrolide immunosuppressant	Phase II
6. 5G1.1	Alexion	Humanized MAb to the C5 protein	Phase II
7. IDEC-131	IDEC/Eisai	Humanized MAb that targets gp39 molecules (CD40 ligand, CD40L) on helper T cells	Phase II
8. Lupus-AHP	EluSys	Bispecific MAb that removes double-stranded DNA autoantibodies	Preclinical
9. CBP-2011*	InKine		Preclinical
10. Anti-BLys	Human Genome Sciences	MAb to B lymphocyte stimulator	Preclinical
11. TACI-Ig	ZymoGenetics	Soluble form of the TACI receptor	Preclinical



(1)



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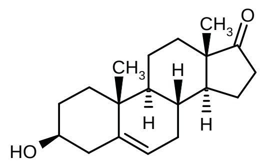
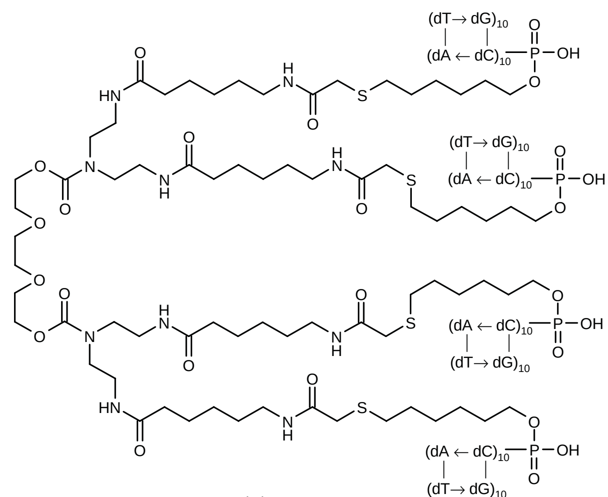


(3)



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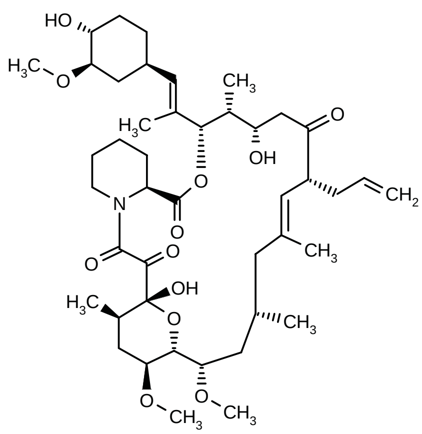

(5)

*Structure not yet detected.

organ-threatening disease show pathogenic antibodies to native double-stranded DNA (dsDNA), particularly those patients with renal dysfunction (2, 3, 5).

In SLE, the polyclonal B cell hyperactivity observed is specifically induced by cognate autoreactive helper T (Th) cells. Although complement activation can play a role in injury caused by immune complex-mediated disease, evidence now suggests that an intact complement cascade is not always required for injury while antibody-effector-cell interactions via the Fc receptor are necessary (6-10). Moreover, several cytokines such as interleukins, platelet activating factor (PAF) and monocyte chemoattractant protein (MCP) have been demonstrated to be involved in organ injury due to SLE.

Due to the complexity of SLE and multiorgan involvement, the treatment of the disorder remains a significant challenge for clinicians. At present, very few agents have been specifically developed for the treatment of SLE and even fewer have reached clinical testing phases. Typically, agents are designed to interfere with immunological processes such as cytokine activation (*e.g.*, upregulation of TGF-β) and modulation (*e.g.*, downregulation of IL-10), T cell activation/T cell-B cell interactions (*e.g.*, CTLA4-Ig and anti-CD40 monoclonal antibodies), production of anti-dsDNA antibodies and complement activation and deposition. Other interventions are gene therapy, stem cell transplantation and preclinical compounds that alter chemokine and/or adhesion molecule expression or regulate apoptosis. Those agents available and currently under development for the treatment of SLE are shown in Table I. One such agent is abetimus sodium (LJP-394), a B cell toleragen that induces tolerance (*i.e.*, unresponsiveness) of specific B cells to immunogen via cross-linking of surface antibodies without providing the second required T cell activating signal. The result is downregulation of anti-dsDNA antibody production from these cells (1). The agent has shown immunomodulatory effects and has been chosen for further development as a treatment for SLE.

Pharmacological Actions

LJP-394 was not immunogenic or antigenic in 4 strains of mice (A/J, C56BL/6, Balb/C, CBA/J). Moreover, it was not antigenic *in vitro* in studies using peripheral blood lymphocytes (PBL) from normal and SLE human donors. In a study using C57BL/6 mice immunized with a synthetic ds-oligonucleotides ([CA]25.[TG25])-KLH conjugate (dsON), LJP-394 treatment (starting 3 weeks after priming and 1 week before boosting) was shown to significantly and dose-dependently reduce the number of anti-dsON antibody-forming spleen cells (> 80%), thus rendering animals unresponsive to further challenges with an immunogenic form of the oligonucleotide. The agent also decreased serum anti-dsON antibody levels by greater than 80%; anti-KLH antibodies were not altered by treatment (1, 11).

LJP-394 treatment (30, 100 and 300 μg/mouse i.v. once or three times/week starting at 9 weeks of age) was also effective in a BXBS murine model of SLE, where anti-dsDNA ELISA slopes were significantly lowered by 60, 74 and 77% for the respective LJP-394 doses and anti-dsDNA antibody-forming cells were significantly reduced by 59%. Treatment had no effect on anti-histone levels but also decreased proteinuria and significantly increased survival. (11).

Pharmacokinetics

A selective HPLC/UV method incorporating a column switching technique for determination of LJP-394 in plasma and serum has been developed. This method was validated using a quantitation range of 10-1000 mg/ml and 10-2600 μg/ml in human and monkey plasma, respectively (12).

Clinical Studies

The safety and immunological effects of LJP-394 (100 mg i.v. over 2 h or as a bolus) were examined in a phase I/II study involving 4 women with stable SLE also receiving prednisone and/or hydroxychloroquine who were followed for 4 weeks. Treatment was well tolerated with none of the patients experiencing serious or severe adverse events. Adverse events reported (*e.g.*, headache, insomnia, worsening of rash) were concluded to be related to the disease and not to treatment. No changes in prothrombin time (PT) or APTT were observed. Some transient complement split products were detected. All patients exhibited a prompt reduction in anti-dsDNA antibody titers. At 4 weeks postdosing, anti-dsDNA antibody levels of 2 patients returned to baseline levels while levels of the other 2 remained 15 and 56% below baseline, respectively (13) (Box 1).

The safety and efficacy of LJP-394 (1, 10 or 50 mg i.v. once or twice weekly or once/month) was further shown in a multicenter, partially randomized, placebo-controlled, double-blind, dose-ranging phase II trial conducted in 58 patients with inactive or mild SLE and elevated anti-dsDNA antibody titers (15 IU/ml or greater). The trial included a 2 week pretreatment period, 16 weeks of dosing with patients receiving 17, 9 or 5 doses and a 2-month postdosing period. The incidence of adverse events was similar in the placebo (89%) and LJP-394 (98%) groups. Of the 49 patients receiving LJP-394, 7 discontinued due to adverse events. With the exception of 1 case of severe rash possibly related to treatment, no serious or severe adverse events were reported. The greatest reductions in anti-dsDNA antibody titers were seen in patients receiving LJP-394 at doses of 50 mg/week (38.1 and 37.1% for weeks 16 and 24, respectively); reductions were noted at week 8 and were sustained throughout the study period. In addition, at week 24, those patients receiving 10 mg/week LJP-394 displayed a mean reduction in anti-dsDNA antibodies of 29.3% (14) (Box 2).

Analysis of serum samples from 230 patients with SLE participating in a double-blind, placebo-controlled trial (described in detail below), demonstrated that patients with elevated anti-dsDNA antibodies found to have a high affinity for the LJP-394 epitope, measured prior to LJP-394 administration using a previously developed assay (15), displayed a significant decrease in affinity over a 4-month, weekly LJP-394 (100 mg i.v.) dosing period. The affinity of dsDNA antibodies to the LJP-394 epitope in patients receiving placebo remained stable throughout the dosing period. Significant treatment-induced reductions in anti-dsDNA were observed in those patients (89%) involved in the double-blind trial with a high affinity of anti-dsDNA for LJP-394 (initial K_d value of 0.8 mg/ml or less). Results indicate that predications can be made as to which SLE patients would most likely

Box 1: Effect of abetimus on dsDNA antibody titers (13) [Prous Science Integrity database].

Design	Open clinical study
Population	Patients with systemic lupus erythematosus (n = 4)
Treatments	Abetimus, 100 mg i.v. infusion x 2 h s.d. (n = 2) Abetimus, 100 mg i.v. bolus s.d. (n = 2)
Results	dsDNA antibody absolute values (% of DNA binding) @ 8 h: A (–106.8); @ 28 d: A (–238.8) dsDNA antibody absolute values (% of DNA binding), change @ 8 h: A (–137.4); change @ 28 d: A (–5.4)
Conclusions	Abetimus was safe and effective in lowering dsDNA antibodies in patients with systemic lupus erythematosus

Box 2: Safety and efficacy of abetimus in SLE patients (14) [Prous Science Integrity database].

Design	Multicenter, randomized, double-blind, placebo-controlled, crossover, dose-finding clinical study
Population	Patients with systemic lupus erythematosus and renal failure (n = 58)
Treatments	Abetimus, 1 mg i.v. infusion 1x/wk x 17 wks (n = 13) Abetimus, 1 mg i.v. infusion 2x/wk x 18 wks (n = 13) Abetimus, 1 mg i.v. infusion 1x/mo x 5 mo (n = 13) Abetimus, 10 mg i.v. infusion 1x/wk x 17 wks (n = 18) Abetimus, 10 mg i.v. infusion 2x/wk x 18 wks (n = 18) Abetimus, 10 mg i.v. infusion 1x/mo x 5 mo (n = 18) Abetimus, 50 mg i.v. infusion 1x/wk x 17 wks (n = 18) Abetimus, 50 mg i.v. infusion 2x/wk x 18 wks (n = 18) Abetimus, 50 mg i.v. infusion 1x/mo x 5 mo (n = 18) Placebo (n = 9)
Withdrawals	A: 9/49 (18.4%) [adverse events 7/49 (14.3%), others 2/49 (4.1%)
Adverse Events	A: 7/49 (14.3%) [multiorgan nonrenal flares 2/49 (4.1%), hematuria and hypertension 1/49 (2.1%), rash 1/49 (2.1%), nephritis 1/49 (2.0%), cellulitis 1/49 (2.0%), herpes zoster 1/49 (2.0%), red blood cell casts in urine 1/49 (2.0%)]
Results	dsDNA antibody titer in the weekly dosing, change @ 16 wks: A50 (–38.1) > A10 (–10%) > P (1%) > A1 (12%); @ 24 wks: A50 (–37%) > A10 (–28%) > A1 (–5%) > P (–4%) dsDNA antibody titer in the biweekly dosing, change @ 16 wks: A50 (8%) > A1 (10%) > P (15%) > A10 40%); @ 24 wks: A50 (10%) > A1 (15%) > A10 (25%) > P (35%) dsDNA antibody titer in the monthly dosing, change @ 16 wks: A1 (–18%) > A10 (–3%) > A50 (–2%) > P (18%); @ 24 wks: A10 (–2%) > A50 (2%) > A1 (5%) > P (10%)
Conclusions	Abetimus was safe and reduced dsDNA antibodies in systemic lupus erythematosus

Box 3: Affinity of antibodies for abetimus in SLE patients (16) [Prous Science Integrity database].

Design	Placebo-controlled clinical study
Population	Patients with systemic lupus erythematosus and renal failure (n = 145)
Treatments	Abetimus, 100 mg 1x/wk x 4 mo (n = 70) Placebo (n = 75)
Results	Antibody affinity reduction rate (%) @ 4 mo: A > P [p = 0.001]
Conclusions	Abetimus reduced antibody affinity in patients with systemic lupus erythematosus and renal failure

respond to LJP-394 by examination of the affinity of anti-dsDNA antibodies to the LJP-394 epitope (16, 17) (Boxes 3 and 4).

Results of a double-blind, placebo-controlled trial conducted in 230 patients with SLE, elevated anti-dsDNA antibodies and history of renal flare showed that fewer renal flares (*i.e.*, reproducible increases in serum creatinine, proteinuria or hematuria) were observed in those patients treated with LJP-394 (100 mg/week i.v. for 16 weeks followed by intermittent dosing with 50 mg for 60

Box 4: Affinity of antibodies for abetimus in SLE patients (17) [Prous Science Integrity database].

Design	Randomized, placebo-controlled, double-blind clinical study
Population	Patients with systemic lupus erythematosus and dsDNA antibodies > 15 IU/ml (n = 211)
Treatments	Abetimus, 100 mg i.v. infusion 1x/wk x 4 mo (n = 70) Placebo (n = 75)
Results	Binding constant (Kd; mg/IgG/ml serum) @ baseline: A (0.41) ≥ P (0.39); @ 4 mo: A (0.84) > P (0.46)
Conclusions	Abetimus appeared to provide clinical benefit in systemic lupus erythematosus patients with high-affinity antibodies for the drug

Box 5: Renal flares in abetimus-treated SLE patients (18) [Prous Science Integrity database].

Design	Double-blind, placebo-controlled clinical study
Population	Patients with systemic lupus erythematosus and renal failure (n = 230)
Treatments	Abetimus, 100 mg i.v. infusion 1x/wk x 16 wks → Abetimus, 50 mg 1x/wk x 60 wks Placebo
Results	Pretreatment high-affinity antibodies rate (%): 89 Renal flares recorded in the high-affinity subpopulation (No.) @ 16 wks: P (21) > A (7) [p = 0.01] Time to renal flares in the high-affinity subpopulation @ 16 wks: A > P [p < 0.01] Exposure to high-dose corticosteroid and cyclophosphamide @ 16 wks: P > A [p = 0.05] Exposure to high-dose corticosteroid and cyclophosphamide in the high-affinity subpopulation @ 16 wks: P > A [p < 0.01]
Conclusions	Abetimus appeared to provide clinical benefit in patients with systemic lupus erythematosus with impaired renal function and high-affinity antibodies for the drug

Box 6: Effect of abetimus in SLE patients with impaired renal function (19) [Prous Science Integrity database].

Design	Double-blind, randomized, placebo-controlled clinical study
Population	Patients with systemic lupus erythematosus and renal failure (n = 28)
Treatments	Abetimus x 60 wks (n = 17) Placebo (n = 11)
Results	Renal flares recorded rate (%) @ 60 wks: P (55.0) > A (18) High-affinity antibodies to drug rate (%): P (10/10 [100]) > A (11/16 [68.7])
Conclusions	Abetimus proved to be of clinical benefit in systemic lupus erythematosus patients with impaired renal function

weeks) as compared to placebo. Treatment was well tolerated. The study was terminated when 19 and 23 patients treated with LJP-394 and placebo, respectively, experienced renal flare. Of those patients with initial anti-dsDNA antibodies showing a high affinity for the LJP-394 epitope (89%), significantly fewer LJP-394 patients experienced renal flares (7 *vs.* 23) and time to renal flare was significantly longer in these patients as compared to placebo. In addition, significantly more LJP-394-treated patients in the intent-to-treat and high-affinity anti-dsDNA antibody populations required less high-dose corticosteroid and cyclophosphamide treatment (18) (Box 5).

Further analysis was performed on a subgroup of 28 patients with renal impairment at baseline (serum creatinine = 1.5 mg/dl at entry) participating in this trial. Of these patients, 32% experienced renal flares during the trial as compared to only 18% in the entire cohort. However, analysis of the renally impaired subgroup revealed that only 18% of the LJP-394-treated patients had renal flares as compared to 55% in placebo. Moreover, no renal flares were observed in those patients shown to have anti-dsDNA antibodies with a high affinity to the LJP-394 epitope. Thus, LJP-394 may be an effective treatment for SLE patients with renal impairment and elevated serum creatinine levels (19) (Box 6).

LJP-394 has been designated an orphan drug by the FDA for the treatment of SLE (20). To date, more than 100 patients have been enrolled in a multicenter phase III trial involving over 60 clinical trial sites in the U.S., Canada, Mexico and Europe. Approximately 300 patients with SLE will be included in the trial, which will investigate the potential of LJP-394 to prevent or delay renal flares, reduce the need for high-dose corticosteroids and/or chemotherapy agents and improve quality of life in these patients (21).

Manufacturer

La Jolla Pharmaceutical Co. (US).

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