Safety, pharmacokinetics, and pharmacodynamics of epratuzumab in Japanese patients with moderate-to-severe systemic lupus erythematosus: Results from a phase 1/2 randomized study

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Abstract

Objectives: This 12-week, randomized, double-blind, placebo-controlled, multicenter phase 1/2 study (NCT01449071) assessed the safety, pharmacokinetics, and pharmacodynamics of epratuzumab in Japanese patients with moderate-to-severe systemic lupus erythematosus despite standard of care.

Methods: Twenty patients were randomized 1:1:1:1:1 to placebo or one of four epratuzumab dose regimens (100 mg every other week [Q2W], 400 mg Q2W, 600 mg every week [QW], or 1200 mg Q2W) administered during an initial 4-week dosing period. Adverse events (AEs), pharmacokinetics and pharmacodynamics were assessed.

Results: Nineteen of 20 patients completed the study. All placebo patients and 13 of 16 epratuzumab patients reported ≥1 AE. 2 of 16 epratuzumab patients reported a serious AE. Cmax and AUC, increased proportionally with dose after first and last infusion, t1/2 was similar across groups (~13 days). Epratuzumab treatment was associated with decreased CD22 mean fluorescence intensity in total B cells (CD19⁺CD22⁺) and unswitched memory B cells (CD19⁺IgD⁺CD27⁺). Small-to-moderate decreases were observed in total B cell (CD20⁺) count. Conclusions: Epratuzumab was well-tolerated, with no new safety signals identified. The pharmacokinetics appeared linear after first and last infusions. Treatment with epratuzumab was associated with CD22 downregulation and with small-to-moderate decreases in total B cell count.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multiple clinical manifestations. Autoactive B cells are thought to play a central role in the pathogenesis of the disease [1] and are therefore a key therapeutic target for SLE [2,3]. Several therapeutic approaches have been used to target B cells, including B cell depletion via mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) and modification of B cell activity via alteration of B cell signaling [4].

The B cell surface receptor CD22 has been shown to play an important role in the regulation of B cell function as a component of the B cell receptor (BCR) complex [5]. CD22 is first expressed in the cytoplasm of pro-B and pre-B cells, and is subsequently expressed at the cell surface as B cells mature, with expression ceasing upon B cell differentiation into plasma cells [6]. Targeting CD22 therefore offers a distinct mechanism for the regulation of BCR activity and B cell function [7], with the potential to limit autoimmune amplification [8].

Epratuzumab is a CD22-targeted monoclonal antibody which is in development for the treatment of SLE. Binding of epratuzumab to CD22 is currently thought to promote the inhibitory function of CD22 on the BCR, inhibiting B cell activation [9,10]. However, the full mechanism of action of epratuzumab has not yet been elucidated. In vitro, epratuzumab has been shown to both stimulate rapid CD22 internalization from the surface of B cells [11] and reduce the levels of multiple B cell surface antigen receptor-modulating proteins (including CD22, CD19, and CD21) via trogocytosis [12]. Overall, in vitro studies carried out to date suggest that modulation of BCR activation may be the dominant mechanism of epratuzumab, with depletion pathways such as ADCC playing a minor role [7].

The safety and efficacy of epratuzumab in patients with SLE were assessed in the phase III ALLEVIATE-1 and -2 randomized controlled trials (RCTs; NCT00111306 and NCT00383214), and...
in the phase IIb EMBLEM™ RCT (NCT00624351) [13–15]. To date, results from these trials have shown that epratuzumab treatment is associated with improvements in disease activity in patients with moderate-to-severe SLE, with an acceptable safety/tolerability profile and moderate reductions in B cell levels [13–15]. Here, we present results from the SL0026 study (NCT01449071), which evaluated the safety, pharmacokinetics, and pharmacodynamics of epratuzumab in Japanese patients with moderate-to-severe general SLE, despite standard of care treatments.

Methods

Patients

Eligible patients were Japanese, aged 18–65 years and diagnosed with SLE as defined by the American College of Rheumatology (ACR) (≥4 criteria met; or if positive for the Neurologic Disorder criterion ≥5 ACR criteria must have been met). All patients had active, moderate-to-severe SLE at screening (14 days prior to Week 0), as demonstrated by British Isles Lupus Assessment Group (BILAG) Grade A disease activity in ≥1 body system or BILAG Grade B disease activity in ≥2 body systems, and a total Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≥6. Inclusion criteria also required that patients were positive for anti-nuclear antibodies (titer ≥1:80) or anti-dsDNA at screening, and had received a stable dose of oral corticosteroids (5–60 mg/day prednisolone equivalent dose) for at least 5 (±1) days prior to Week 0. Patients who received immunosuppressants, bromocriptine, danazol, dapsone, or retinoids must have been on a stable dose prior to the administration of placebo or study drug at Week 0 (anti-malarials are not approved for the treatment of SLE in Japan). Exclusion criteria included active, severe, neuropsychiatric, or renal SLE (defined by BILAG Grade A renal activity), or a history of chronic infections.

Study design

SL0026 was a phase 1/2, randomized, double-blind, placebo-controlled, multicenter study, which was initiated at 11 sites in Japan. The primary objective of this study was to evaluate the safety, tolerability, and pharmacokinetics of epratuzumab in Japanese subjects with moderate-to-severe SLE, despite standard of care treatments. Secondary objectives included assessment of the overall levels of monocytes, NK, B, and T cells in the peripheral blood circulation over time following epratuzumab treatment and assessment of the immunogenicity of epratuzumab treatment.

The study consisted of a single 12-week treatment cycle, which comprised a 4-week dosing phase followed by an 8-week observation phase (Figure 1). Eligible patients were assigned to a treatment regimen based on a predetermined randomization schedule. Patients were randomized in a 1:1:1:1:1 ratio to placebo or one of four fixed doses of intravenous (IV) epratuzumab: 100 mg every other week (Q2W), 400 mg Q2W, 600 mg every week (QW), or 1200 mg Q2W (with 600 mg QW and 1200 mg Q2W corresponding to the same cumulative dose of 2400 mg).

All patients, investigators, and their staff, and sponsor clinical teams and their delegates remained blinded to treatment assignment during the clinical conduct of the study. The epratuzumab 100, 400, and 1200 mg Q2W doses were administered as infusions of active drug at Weeks 0 and 2 and placebo at Weeks 1 and 3, to maintain study blinding. The study protocol was reviewed by the Institutional Review Board and all patients provided informed consent before study enrolment. This study was conducted based on Good Clinical Practice and the Declaration of Helsinki.

Study drug

Epratuzumab was supplied at a concentration of 10 mg/mL, filled in sterile glass vials for slow IV infusion, using only phosphate-buffered saline (PBS) with 0.02% polysorbate as a vehicle/buffer for the infusion procedure. Placebo treatment was supplied as sterile 0.04 M PBS with 0.02% polysorbate 80.

Safety and tolerability

Safety analyses were carried out on the Safety Set, which included all randomized patients who received at least 1 dose or partial dose of study drug. Treatment-emergent adverse events (AEs) and serious AEs (SAEs) were assessed at each visit throughout the study.

Pharmacokinetic assessments

Pharmacokinetic analyses were carried out in the Pharmacokinetic Set, which included all Safety Set patients who were randomized to an epratuzumab treatment arm, had at least 1 pharmacokinetic measurement, and had no important protocol deviations. Blood samples were collected for the analysis of epratuzumab plasma concentrations at Weeks 0, 1, 2, 3, 4, 6, 8, 10 and 12. Samples were collected once at each non-dosing visit and three times at each dosing visit (pre-dose, end of infusion, and 30 min post-infusion). Plasma concentrations of epratuzumab were determined using a validated enzyme-linked immunosorbent assay method by Eurofins (formerly Merck Millipore, Billerica, MA). The lower limit of quantification (LLOQ) for epratuzumab plasma concentration was 160 ng/mL.

Pharmacokinetic parameters calculated for epratuzumab included: Cmax, the value of the maximum plasma drug concentration directly obtained from the observed concentration versus time curves; AUC0–∞, area under the concentration–time curve over the dosing interval (2 weeks for Q2W dosing regimens, 1 week for QW dosing regimens) and t1/2, the elimination half-life associated with the terminal elimination rate constant (kz), calculated as ln 2/iz.

Human anti-drug antibodies to epratuzumab

Human anti-drug antibodies (ADA) to epratuzumab were measured using a validated electrochemiluminescence-based Meso Scale Discovery assay (Merck Millipore; LLOQ = 31 ng/mL). Blood samples were evaluated for plasma levels of ADA to epratuzumab at baseline and Week 12.

Pharmacodynamic assessments

Pharmacodynamic analyses were carried out in the Pharmacodynamic Set, which consisted of all patients in the Safety Set randomized to either epratuzumab treatment or placebo who had at least 1 pharmacodynamic measurement, and had no important protocol deviations. All pharmacodynamic variables were analyzed by flow cytometry of blood samples taken once at Weeks 0, 1, 2, 3, 4, 8, and 12.

Total cell counts for B cells (CD20+) and T cells (CD3+) were analyzed. To assess CD22 internalization on B cells, CD22 mean fluorescence intensity (MFI) was evaluated on three B cell subsets: total B cells (CD19+CD22+), unswitched memory B cells (CD19+IgD+CD27+), and plasmablast/plasma cells (CD19+CD38+CD27+).

Immunological status

To evaluate general immunological status during epratuzumab treatment, flow markers for monocytes (CD14+), NK cells
(CD16+CD56+CD3+), cytotoxic T cells (CD3+CD8+), and T-helper cells (CD3+CD4+) in peripheral blood circulation were measured by flow cytometry. Immunoglobulin levels (IgG, IgA, and IgM) were also determined from blood samples taken at Weeks 0, 1, 2, 3, 4, 8, and 12.

Statistical analysis
The sample size was not determined through formal statistical calculation. However, it was expected that four patients per treatment group would be sufficient to evaluate pharmacokinetics, based on results from previous epratuzumab studies.

For safety data, the number and percentage of patients who experienced each AE were presented by treatment group and classified by system organ class and preferred term according to the MedDRA dictionary v.15.1.

Epratuzumab plasma concentration–time data were graphically explored, and subjected to a non-compartmental analysis using Phoenix-WinNonlin (version 6.2) and PKS (version 4.0.3). At time points where 2/3 of the data were at or above the LLOQ (160 ng/mL for plasma concentration of epratuzumab), descriptive statistics were calculated and values below the LLOQ replaced by this numerical value of the LLOQ. After non-compartmental analysis, descriptive statistics were calculated if 2/3 of individual pharmacokinetic parameters were available. Missing pharmacokinetic data were not imputed.

For pharmacodynamics and immunological parameters, descriptive statistics over time, including the change and percentage change from baseline for each parameter, were summarized by treatment group and presented graphically.

Results
Patient characteristics
Of 20 randomized patients, 19 (95.0%) completed the study; 1 patient in the 1200 mg Q2W group discontinued due to an SAE. Patient demographics and disease characteristics at baseline were similar across all treatment groups (Table 1). All patients were 18–65 years of age and the majority [17 (85.0%)] were ≥30 years of age; mean age for all patients was 39.9 years (range: 34.8–46.3 years). The majority of patients were females (18 [90.0%]).

Safety and tolerability
All patients on placebo and 13 of 16 patients on epratuzumab reported at least one AE. The majority of patients reported AEs of mild intensity and no severe non-SAEs were reported (Table 2). SAEs were reported in 2 of 16 patients (one case of drug hypersensitivity in the epratuzumab 1200 mg Q2W group, one case of Herpes zoster in the 600 mg QW group). No deaths occurred during the study. A complete list of all AEs in the study by system organ class and preferred term is provided in Supplementary Table 1.

AEs considered by the investigator to be related to study medication were reported in 2 of 4 patients in the placebo group and 7 of 16 patients in the all active doses group. One patient discontinued from the study due to an SAE (1200 mg Q2W group, SAE of drug hypersensitivity), 15 h after the first infusion of study medication. The event was moderate in intensity, led to withdrawal of study medication and discontinuation from the study, and was considered related to study medication by the investigator.

AEs reported in ≥1 patient in the all active doses group were acne and injection site pain. Two events of injection site pain were reported from one patient (100 mg Q2W group) and both were considered as an infusion reaction by the investigator. The first event was reported after the first injection (epratuzumab) and the second after the second injection (placebo). These were local infusion reactions, and no systemic infusion reactions were identified.

There were no consistent clinically meaningful effects of epratuzumab on clinical laboratory parameters, vital signs, body weight, BMI, ECG results, or chest X-ray results. Changes in laboratory parameters were, in general, related to the underlying disease.

Pharmacokinetics
After the final infusion of epratuzumab, plasma concentrations gradually decreased over time, showing apparent linear elimination with similar rates of elimination across all epratuzumab treatment groups (Figure 2) and an elimination half-life of epratuzumab of approximately 13 days across all treatment groups (Table 3). Pharmacokinetics appeared to be linear: after first and last infusion $C_{\text{max}}$ and $AUC_{\text{t}}$ increased proportionally with dose (Table 3). With the current dose regimens, steady state was not achieved as expected from the utilized cyclic dose regimen and the observed $t_{1/2}$ half-life.

Human ADA to epratuzumab
Two patients in the epratuzumab 100 mg Q2W group had detectable concentrations of ADA just above the LLOQ; in all other patients ADA were not seen. The elimination half-life of epratuzumab in these two patients was shorter (approximately 6 days).
Pharmacodynamics

In general, there were small-to-moderate decreases from baseline in total B cell (CD20⁺) counts in all epratuzumab groups throughout the study (Figure 3A); no consistent trends were observed in total T cell (CD3⁺) counts (Figure 3B). There was no clear trend in B cell or T cell counts with dose/regimen over the study following an apparent linear elimination, as shown by similar slopes of elimination across all epratuzumab treatment doses (ranging from 100 to 1800 mg Q2W, and epratuzumab 600 mg QW, all appear to have an acceptable safety profile [13,14]. This is the first report of the safety, pharmacokinetics, and pharmacodynamics of epratuzumab treatment in Japanese patients with moderate-to-severe SLE.

Discussion

Epratuzumab has been administered to more than 500 SLE patients in clinical studies outside of Japan, and further phase 3 studies of epratuzumab are ongoing. Doses of epratuzumab ranging from 100 to 1800 mg Q2W, and epratuzumab 600 mg QW, all appear to have an acceptable safety profile [13,14]. This is the first report of the safety, pharmacokinetics, and pharmacodynamics of epratuzumab treatment in Japanese patients with moderate-to-severe SLE.

No new safety signals were identified in this study and epratuzumab appears to have an acceptable safety profile in adult Japanese patients with moderate-to-severe SLE. These results are similar to previous studies of epratuzumab in patients with moderate-to-severe SLE elsewhere in the world [13,14].

Epratuzumab plasma concentrations gradually decreased during the study following an apparent linear elimination, as shown by the similar slopes of elimination across all epratuzumab treatment

Immunological status

No changes were observed in cell counts for monocytes (CD14⁺), NK cells (CD16⁺CD56⁺CD3⁺), cytotoxic T cells (CD3⁺CD8⁺), and T-helper cells (CD3⁺CD4⁺). For immunoglobulin levels, there was an approximately 10% decrease from baseline in IgM for the epratuzumab treatment and placebo groups; no trends were observed for IgG and IgA.

Table 1. Baseline characteristics and demographics (Safety Set).

| Medication use at baseline | Placebo (n = 4) | 100 mg Q2W (n = 4) | 400 mg Q2W (n = 4) | 600 mg QW (n = 4) | 1200 mg Q2W (n = 4) |
|---------------------------|----------------|-------------------|--------------------|------------------|--------------------|
| Age, years                | 46.3 (13.6)    | 34.8 (10.8)       | 45.5 (5.1)         | 36.0 (7.8)       | 37.0 (9.4)         |
| Female, n (%)             | 4 (100)        | 4 (100)           | 3 (75.0)           | 4 (100)          | 3 (75.0)           |
| Disease duration, years   | 12.1 (9.8)     | 14.8 (12.5)       | 7.7 (6.1)          | 9.7 (4.4)        | 14.8 (4.4)         |
| Anti-malarials, n (%)     | 0              | 1 (25.0)          | 1 (25.0)           | 2 (50.0)         | 0                  |
| Corticosteroids, mg/day   | 18.1 (12.5)    | 12.5 (6.5)        | 15.4 (10.3)        | 11.9 (5.5)       | 13.1 (11.8)        |
| Total BILAG score†        | 22.0 (6.8)     | 21.0 (3.3)        | 22.3 (6.2)         | 18.3 (5.0)       | 25.0 (5.7)         |
| Total SLEDAI score        | 9.0 (2.6)      | 13.0 (3.5)        | 9.5 (1.0)          | 9.5 (1.9)        | 9.3 (2.5)          |

Table 2. Overview of AEs during SL0026 (Safety Set).

| Medication use at baseline | Placebo (n = 4) | 100 mg Q2W (n = 4) | 400 mg Q2W (n = 4) | 600 mg QW (n = 4) | 1200 mg Q2W (n = 4) |
|---------------------------|----------------|-------------------|--------------------|------------------|--------------------|
| Anti-malarials, n (%)     | 0              | 2 (50.0)          | 4 (100)            | 4 (100)          | 3 (75.0)           |
| Corticosteroids, mg/day   | 0              | 0                 | 0                  | 2 (50.0)         | 1 (25.0)           |
| Total BILAG score†        | 0              | 0                 | 1 (25.0)           | 0                | 1 (6.3)            |
| Total SLEDAI score        | 0              | 0                 | 1 (25.0)           | 0                | 0                  |

Data shown are number of patients reporting AEs (%) from the Safety Set, defined as all patients who received at least one dose or partial dose of study medication.

*AEs are classified according to the Medical Dictionary for Regulatory Authorities (MedDRA) v.15.1.
†Two events of injection site pain were reported from one patient and both were considered as an infusion reaction by the investigator. The first event was reported after the first injection (epratuzumab) and the second after the second injection (placebo). These were local infusion reactions, and no systemic infusion reactions were identified.
The characterized elimination half-life was estimated to be approximately 13 days across the treatment groups. This value is in the range of previous epratuzumab studies and in agreement with the expected long half-lives generally seen in monoclonal antibodies of a similar format [16]. Pharmacokinetics appeared to be linear, with \( C_{\text{max}} \) and \( \text{AUC}_{28} \) after first and last infusion increasing proportionally with dose.

A previous study evaluating infliximab treatment of Japanese patients with rheumatoid arthritis revealed an association between the development of anti-infliximab antibodies and infusion reactions [17]. In the present study, among all patients, anti-epratuzumab antibodies were only detected in two patients in the epratuzumab 100 mg Q2W group. These two patients, however, did not experience infusion reactions. Given the small number of patients included in this study, it is still premature to draw conclusions about the immunogenicity of epratuzumab from these results.

**Figure 2.** Epratuzumab plasma concentrations, geometric group means (Pharmacokinetic Set). Geometric means were only calculated if 2/3 of the data were above the limit of quantification (LOQ). Two patients in the 100 mg Q2W group had concentrations that were below the limit of quantification at Week 10 and 12. *One patient in the 1200 mg Q2W group discontinued due to an AE, did not complete one infusion cycle and did not contribute data past Week 0. †Week 2 for Q2W groups, Week 3 for QW group. \( C_{\text{max}} \), area under the concentration–time curve over the dosing interval; \( C_{\text{max}/dose} \), maximum plasma epratuzumab concentration.

| Epratuzumab dose | 100 mg Q2W (n = 4) | 400 mg Q2W (n = 4) | 600 mg QW (n = 4) | 1200 mg Q2W (n = 3)* |
|------------------|------------------|------------------|-----------------|-------------------|
| Geometric means (% coefficient variation) | Geometric means (% coefficient variation) | Geometric means (% coefficient variation) | Geometric means (% coefficient variation) |
| \( C_{\text{max}} \) (ng/mL) | 42049 (20.9) | 149 807 (25.1) | 240 538 (29.4) | 728 577 (6.1) |
| \( C_{\text{max}/dose} \) (ng/mL/mg) | 420 (20.9) | 375 (25.1) | 401 (29.4) | 607 (6.1) |
| \( \text{AUC}_{28} \) (day ng/mL) | 244 709 (34.2) | 867 483 (21.2) | 976 465 (30.9) | 3 219 076 (42.5) |
| \( \text{AUC}_{28}/dose \) (day ng/mL/mg) | 2447.1 (34.2) | 2168.7 (21.2) | 1627.4 (30.9) | 2682.6 (42.5) |
| \( t_{1/2} \) (day) | 10.1 (66.2) | 13.4 (16.6) | 12.7 (21.8) | 14.5 (36.9) |

\( t_{1/2} \), elimination half-life; Q2W, every other week; QW, every week.

*One patient in the 1200 mg Q2W group discontinued due to an AE, did not complete one infusion cycle and did not contribute data past Week 0.
†Week 2 for Q2W groups, Week 3 for QW group. \( \text{AUC}_{28} \), area under the concentration–time curve over the dosing interval; \( C_{\text{max}} \), maximum plasma epratuzumab concentration.
For total CD3+ T cell counts, no consistent trends were observed across treatment groups. Additionally, there were no changes observed in the profiles of monocytes (CD14+ cells), NK cells (CD16^CD56^CD3^- cells), cytotoxic T cells (CD3^CD8^ cells), and T helper cells (CD3^CD4^ cells) and there was no evidence that epratuzumab had an effect on immune status. This study included a relatively small sample size and was of short duration; further studies are needed to confirm the long-term effects of epratuzumab in this patient population. However, the results presented here support the further development of epratuzumab in the treatment of Japanese patients with SLE.

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Conflict of interest

T. Tsuru has served as a consultant for UCB Pharma. Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Abbvie, Daiichi-Sankyo, Chugai, Takeda, Mitsubishi-Tanabe, BMS, Astellas, Eisai, Janssen, Pfizer, Asahi Kasei, Eli Lilly, GlaxoSmithKline, UCB Pharma, Teijin, MSD, and Santen and has received research grants from Mitsubishi-Tanabe, Takeda, Chugai, Astellas, Eisai, Taisho-Toyama, Kyowa-Kirin, Abbvie, and BMS. Y. Takasaki has acted as a consultant and/or served on speakers bureau for Santen, Daiichi-Sankyo, Mitsubishi Tanabe, BMS, AstraZeneca, Astellas, MSD, Chugai, Asahi Kasei, Eisai, and Janssen.

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Supplementary material available online