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PAPER

An exploratory dose-escalating study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous atacicept in patients with systemic lupus erythematosus

C Pena-Rossi[1], E Nasonov[2], M Stanislav[2], V Yakusevich[3], O Ershova[3], N Lomareva[4], H Saunders[1], J Hill[5] and I Nestorov[5]

[1]Merck Serono S.A., Geneva, Switzerland; [2]GU Institute of Rheumatology, RAMS, Moscow, Russian Federation; [3]Solovievs Clinical Hospital for Urgent Medical Care, Municipal Health Organisation, Yaroslavl, Russian Federation; [4]City Clinical Hospital No. 25, City Rheumatology Centre, St Petersburg, Russian Federation; and [5]ZymoGenetics, Inc., Seattle, Washington, DC, USA

Atacicept, a recombinant fusion protein containing the extracellular, ligand-binding portion of the transmembrane activator and calcium modulator and cyclophilin-ligand interactor receptor, and the Fc portion of human immunoglobulin (Ig) G, is designed to block the activity of B-lymphocyte stimulator and a proliferation-inducing ligand, and may have utility as a treatment for B-cell-mediated diseases, such as systemic lupus erythematosus (SLE). This Phase Ib study investigated the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of intravenous (i.v.) atacicept in patients with mild-to-moderate SLE. Patients (n = 24) were randomised (5:1) to receive atacicept (single dose: 3, 9 or 18 mg/kg; or multiple dose: 2 × 9 mg/kg) or matching placebo. Patients were followed for 6 weeks after dosing (9 weeks in the 2 × 9 mg/kg cohort). Local tolerability of atacicept was comparable with that of placebo, with only mild injection-site reactions reported with atacicept. Atacicept i.v. was generally well tolerated, both systemically and locally, in patients with mild-to-moderate SLE. Atacicept displayed non-linear PK, which was predictable across doses and between single and repeat doses. The biological activity of atacicept was demonstrated by its marked effect in reducing B-cells and Ig levels in patients with SLE. This supports the utility of this therapeutic approach in the treatment of autoimmune diseases, such as SLE. *Lupus* (2009) **18,** 547–555.

Key words: APRIL; atacicept; biological agents; BLyS; systemic lupus erythematosus; TACI-Ig

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that primarily affects women.[1] The symptoms of SLE affect many different parts of the body, including the joints, skin, blood, brain and kidneys, and its effects can be fatal.[1,2] Historically, hydroxychloroquine sulphate and corticosteroids, together with varying combinations of immunosuppressants, have been the main treatments for SLE.[3] These therapies have been associated with poor safety profiles and/or low response rates, leading to a high unmet therapeutic need among patients with SLE.[3,4]

Correspondence to: Claudia Pena-Rossi, Merck Serono S.A., Chemin des Mines 9, 1202 Geneva, Switzerland.
Email: claudia.penarossi@merckserono.net
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Recent developments in genetic and immunological techniques have advanced our understanding of the basic molecular and cellular processes underlying the pathogenesis of SLE.[5–7] This has led to the development of a new generation of SLE therapies designed to target specific steps in the disease process.[8–13] It is hoped that these new, targeted therapies, when compared with conventional SLE treatments, will have improved safety profiles and similar or improved efficacy.

SLE is characterised by the production of anti-nuclear antibodies (ANA),[2] which are thought to play a central role in the disease, targeting healthy tissues throughout the body. The origin of ANA is unclear, but may involve B-cell hyperresponsiveness.[6] Abnormal T-cell behaviour, complement deficiencies and abnormal cytokine function are also thought to play a role in SLE.[5–7]

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The involvement of B-cells in autoantibody production has lead to numerous investigations into B-cell receptor signalling in patients with SLE.[14] B-lymphocyte stimulator (BLyS; also known as B-cell-activating factor of the tumour necrosis factor [TNF] family [BAFF]) and a proliferation-inducing ligand (APRIL) are two related members of the TNF ligand superfamily that both regulate B-cell maturation, function and survival.[15–17] Experiments in animals and humans suggest a role for these molecules in SLE. Transgenic mice engineered to express high levels of BLyS exhibit an expanded peripheral B-cell compartment, with considerably increased numbers of mature B-cells.[18,19] In addition, these mice show autoimmune-like manifestations, including high levels of immunoglobulins (Igs), rheumatoid factors and anti-DNA autoantibodies, proteinuria and glomerulonephritis, characteristic of SLE-like symptoms.[18,19] Furthermore, increased levels of BLyS correlate with the onset and progression of disease in these mice.[18] In humans, elevated levels of APRIL, BLyS and/or BLyS/APRIL heterotrimers have been detected both in patients with SLE[20,21] and in patients with other autoimmune diseases.[21–24]

BLyS and APRIL share signalling through the transmembrane activator and calcium modulator and cyclophilin-ligand interactor (TACI) and B-cell maturation antigen (BCMA) receptors.[25,26] In addition, BLyS has a high affinity for the BAFF receptor (BAFF-R),[26,27] and APRIL can bind with low affinity to heparin-sulphate proteoglycans.[28,29] Atacicept (formerly known as TACI-Ig) is a recombinant fusion protein containing the extracellular, ligand-binding portion of the TACI receptor and the Fc portion of human IgG.[18] Atacicept binds to BLyS and APRIL, and inhibits their effects on B-cells. Experiments in mice have demonstrated that atacicept reduces mature B-cell counts and serum antibody levels in normal mice[30] and delays disease progression in a mouse model of SLE.[18]

Overall, this evidence suggests that atacicept has potential utility in the treatment of SLE, and a clinical development programme to investigate the use of atacicept in SLE has been initiated. A Phase Ia study demonstrated that a single subcutaneous dose of atacicept (up to 630 mg) is well tolerated in healthy volunteers.[31] Single and multiple doses of subcutaneous atacicept were well tolerated in exploratory studies, where biological effects in line with the proposed mechanism of action (MoA) of atacicept were observed in patients with rheumatoid arthritis.[32] Here, we describe a Phase Ib study investigating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (i.v.) atacicept in patients with SLE.

Methods

Study design

We conducted a double-blind, randomised, placebo-controlled, sequential, dose-escalating, exploratory Phase Ib study (protocol number: 25842) at three centres in Russia. The primary objective of the study was to evaluate the safety, tolerability, PK and PD of single or multiple i.v. injections of atacicept in patients with mild-to-moderate SLE.

The study protocol was approved by the local independent ethics committee or institutional review board at each centre, and the study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki (2000). All patients gave written informed consent prior to entry into the study.

On enrolment, patients were assigned to four sequential cohorts (Figure 1). A different atacicept dose (single or multiple i.v. injection) was investigated in each cohort. Patients within each cohort were randomised 5:1 to atacicept or matching placebo and followed for 6 weeks after dosing (9 weeks in the 2×9 mg/kg cohort). Prior to each dose escalation, safety and tolerability data at 2 weeks post-dose were assessed by a safety review board. The dosing regimen and dose-escalation scheme were selected based on the design and results of the Phase I trial of atacicept in healthy volunteers.[31]

Patients

We recruited patients aged 18–70 years, with a body mass index <40 kg/m^2 and with a proven diagnosis of mild-to-moderate SLE. Patients were required to meet at least four of the American College of Rheumatology (ACR) criteria for SLE classification[33] and have a score of 0–10 on the SLE Disease Activity Index (SELENA SLEDAI).[34] Patients were excluded if they had received immunosuppressive drugs (e.g. azathioprine, cyclosporine, methotrexate,

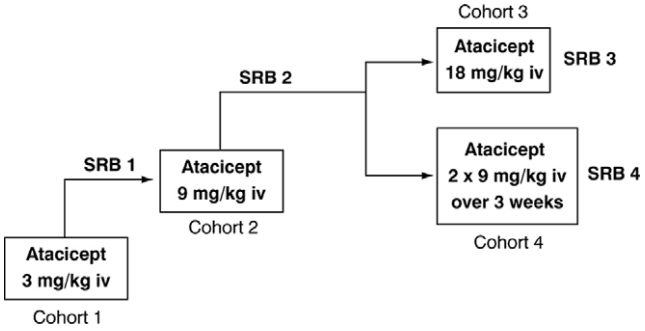

Figure 1 Patient cohorts and dose-escalation scheme. i.v., intravenous; SRB, safety review board.

cyclophosphamide, mycophenolate mofetil, leflunomide) during the 8 weeks prior to the study, prednisone >20 mg/day, hydroxychloroquine >400 mg/day, non-steroidal anti-inflammatory drugs, a change in dose regimen during the 4 weeks prior to the study or previous therapy with other biological therapies. Patients were excluded if they had severe renal disorder, neurological symptoms suggestive of significant central nervous system involvement, significant impairment of liver function, active acute infective illness (reactivation of Epstein-Barr virus), chronic serious infectious disease (e.g. tuberculosis) or opportunistic infections. Patients were also excluded if they had positive serology results for hepatitis B surface antigen, hepatitis C virus or human immunodeficiency virus, a medical history of congestive heart failure or cancer, clinically significant abnormalities in haematological tests or clinically significant serious abnormalities on chest X-ray or electrocardiogram (ECG). Women who were pregnant or breastfeeding were excluded from the study.

Assessments

Scheduled visits

For single-dose cohorts (Cohorts 1–3), scheduled visits took place on days 2, 3, 4, 8, 15, 22 and 29, with a post-study visit on day 43. For the repeat-dose cohort (Cohort 4), scheduled visits took place on days 2, 3, 4, 8, 21, 29, 36, 43 and 57, with a post-study visit on day 64.

PK/PD assessments

In Cohorts 1–3, serum samples for PK/PD measurements were taken before dosing, 15 minutes, 30 minutes and 4 hours post-dose, and at each subsequent scheduled visit thereafter. In Cohort 4, serum samples for PK/PD measurements were taken before dosing, 30 minutes and 4 hours post-dose, and at each subsequent scheduled visit thereafter (with the exception of the visit on day 36). Patients in Cohorts 3 and 4 also returned on days 84 and 120 for PK/PD sampling.

PK was assessed by measuring serum levels of free atacicept, atacicept•BLyS complex and total atacicept (defined as free atacicept + atacicept•BLyS complex) quantified using enzyme-linked immunosorbent assay. Serum was incubated with a biotin-conjugated monoclonal antibody specific for atacicept (free or total atacicept detection) or BLyS (atacicept•BLyS complex detection) and immobilised on a streptavidin-coated microplate. After washing, an atacicept-specific monoclonal antibody conjugated to horseradish peroxidase (HRP) was added. For detection of total atacicept, a BLyS-specific monoclonal antibody conjugated to HRP was also added at this stage. In all three assays, atacicept species were detected and quantified using standard chemiluminescence methods.

PD was assessed by measuring serum levels of Igs (IgG, IgM, IgA) and lymphoid cell populations in peripheral blood. Igs were measured using standard methods. Four-colour immunophenotyping, using standard flow cytometry methods, was used to identify the following cell types: total T-cells (CD3+, CD45+), T-helper cells (CD8–, CD3+, CD4+, CD45+), T-cytotoxic/suppressor cells (CD4–, CD3+, CD8+, CD45+), total B-cells (CD19+), mature B-cells (CD19+, CD27–, IgD+), naïve B-cells (CD38–, CD27–, CD19+, CD20+), memory B-cells (CD38–, CD19+, CD20+, CD27+), monocytes (CD14+, CD45+) and natural killer (NK) cells (CD3–, CD45+, CD56+). Peripheral blood was collected from patients at the clinical sites and transported to a contract research organisation within 24 hours. Whole blood was incubated with appropriate dilutions of directly labelled fluorescent antibodies and red blood cells were lysed using a standard cell-lysing reagent. Counting beads were used to determine total T- and B-cell concentrations. Approximately 100,000 events were collected and analysed using flow cytometry analysis software. For data analysis, a lymphocyte gate was used for T- and NK-cell determinations, and a lymphocyte and monocyte gate was used for B-cell subset determinations.

Levels of complement-3 (C3) and ANA, including anti-dsDNA antibodies, were measured as markers of SLE disease activity. C3 levels were measured using standard methods, and ANA were measured using the AtheNA Multi Lyte® ANA test system (Zeus Scientific Inc., Raritan, NJ, USA). Pre-dose BLyS serum concentrations were also measured during this study.

Safety and tolerability

A physical examination, including measurement of vital signs, was conducted at screening, before and 4 hours after dosing, and at each subsequent visit. For Cohorts 1–3, standard 12-lead resting ECGs were performed at screening, before dosing on day 1 and on days 2, 15, 29 and 43. For Cohort 4, ECGs were performed at screening, before dosing on day 1, on day 2, before and 30 minutes post-dose on day 21 and on days 36 and 64.

The incidence, severity and relationship to treatment of adverse events (AEs) were assessed throughout the study. The incidence of any injection-site pain, itching, tenderness, swelling, redness or bruising were assessed regularly by the investigator (any other local reactions were also noted). Pain was patient-graded using a 10-cm visual analogue scale. Concomitant medication usage was recorded throughout the study.

Laboratory analyses (haematology, blood chemistry, coagulation, urinalysis) were conducted at the screening visit, prior to dosing on day 1, and on days 2, 8, 15, 22, 29 and 43 in Cohorts 1–3, and at the screening visit, prior to dosing on day 1, on days 2 and 8, before and 30 minutes post-dose on day 21, and on days 36 and 64 in Cohort 4.

Vaccine immunisation status was assessed by measuring tetanus toxoid antibody titres on day 1 and at the final post-study visit (patients in Cohort 4 were also assessed on day 29). Assays for binding and neutralising antibodies to atacicept were performed on samples taken on day 1 and at the final post-study visit; patients in Cohort 4 also had an assessment 30 minutes post-dose on day 21.

Statistical analyses

Due to the exploratory nature of this study, sample size determination was not based on any formal statistical assumptions. Six patients were to be included at each dose level, with five receiving active medication and one receiving placebo. This number of patients was considered sufficient to allow an initial assessment of the systemic and local tolerability of atacicept and to allow a description of its PK and PD properties.

All analyses were performed on the safety analysis set (all patients who received at least one dose of study medication) using an as-treated approach. Results were summarised for the combined placebo group, for atacicept recipients in each cohort and for the overall trial population. Continuous variables were tabulated using summary statistics (number of observed values, number of missing values, mean, standard deviation, median, minimum and maximum). Categorical variables were summarised using frequencies and percentages. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 8.0), and treatment-emergent AEs (those with onset between the first treatment injection and the post-study follow-up visit) were summarised by System Organ Class and Preferred Term. Concomitant medications were coded using WHO-Drug (March 2006) by ATCtext4 and ATCtext2. ATCtext2 was used in place of ATCtext4 for medications for which no ATCtext4 classification was given.

Concentration–time profiles for PK data were subjected to non-compartmental analysis using WinNonLin software (version 5.0.1), and the resulting values were summarised statistically.

Results

Patients

Of the 32 patients who were screened, 24 patients were enrolled in the study and randomised into four cohorts (six patients per cohort). All 24 patients completed the trial.

Baseline demographic and clinical characteristics were well balanced between groups (Table 1). All patients were White, the vast majority were female (92%) and the median age was 45.5 years. Median disease duration was 6.0 years, and patients generally showed characteristics of mild-to-moderate SLE, with signs and symptoms affecting a wide range of organ systems. Overall, all patients (100%) satisfied at least four of the 11 ACR criteria for SLE; 38% of patients satisfied four ACR criteria, 42% satisfied five criteria, 13% satisfied six criteria and 8% satisfied seven criteria. Baseline SLE clinical manifestations based on the ACR criteria included: arthritis (91.7%), photosensitivity (66.7%), malar rash (58.3%), oral ulcers (16.7%), serositis (12.5%), haematological manifestations (33.3%), discoid lupus

Table 1 Baseline demographic and clinical characteristics of patients involved in the study

	Placebo (n = *4*)	*Atacicept 3 mg/kg* (n = *5*)	*Atacicept 9 mg/kg* (n = *5*)	*Atacicept 18 mg/kg* (n = *5*)	*Atacicept 2 × 9 mg/kg* (n = *5*)	*All* (n = *24*)
Age, years	44.0 (21–54)	54.0 (25–66)	45.0 (32–64)	41.0 (34–60)	47.0 (36–55)	45.5 (21–66)
Sex, *n* (%) female	4 (100)	4 (80)	5 (100)	4 (80)	5 (100)	22 (92)
BMI, kg/m^2	24.63 (20.7–35.2)	27.53 (22.9–39.6)	24.09 (17.7–31.2)	29.45 (24.0–36.0)	25.46 (20.1–32.8)	26.57 (17.7–39.6)
Number of ACR[33] criteria met						
4	1	1	3	2	2	9
5	3	4	0	1	2	10
6	0	0	1	1	1	3
7	0	0	1	1	0	2
Disease duration, years	4.5 (3–27)	7.0 (4–33)	5.0 (4–12)	14.0 (3–20)	14.0 (5–28)	6.0 (3–33)
SELENA SLEDAI score[34]	0.00 (0.0–4.0)	0.00 (0.0–4.0)	0.00 (0.0–1.0)	0.00 (0.0–3.0)	0.00 (0.0–4.0)	0.00 (0.0–4.0)

Abbreviations: ACR: American College of Rheumatology; BMI: body mass index; SELENA SLEDAI: systemic lupus erythematosus Disease Activity Index.
All data are presented as median (range, min–max) unless specified otherwise.

(41.7%) and renal involvement (25.0%). In line with the trial entry criteria, no patients had neurological disorders at baseline.

A total of 71% of patients were receiving corticosteroids and 58% of patients were receiving hydroxychloroquine or chloroquine. No use of other immunosuppressive agents was reported during the trial.

Safety

Total cumulative exposure ranged from 182 to 1735 mg per patient in the atacicept groups, and the median cumulative dose reflected the assigned dose level in each cohort (3 mg/kg: 201 mg; 9 mg/kg: 612 mg; 18 mg/kg: 1440 mg; 2 × 9 mg/kg: 1278 mg).

During the study, 15 treatment-emergent AEs were reported in 10 patients (Table 2). All AEs were mild (12 events) or moderate (three events) in severity. AEs were reported most frequently in the System Organ Class of infections and infestations (four events in four patients). All infection-related events were considered to be unrelated to trial medication. Of the 15 AEs that were reported, four were considered possibly or probably related to study medication: three reports of decreased white blood cell (WBC) count and one report of pyrexia. The decreased WBC counts occurred in two patients who received 2 × 9 mg/kg atacicept, both of whom had low WBC counts before dosing on study day 1. WBC counts had recovered by the end of the study. There were no infections or other AEs reported for these two patients. All three AEs reported in the placebo group occurred in the same patient. One serious event was reported, which was considered unrelated to trial medication: a subcutaneous abscess of the ear in a patient with a long-standing history of an ear cyst. The abscess resolved following surgical and antibiotic treatments. No deaths were reported, and no AEs led to treatment or study discontinuation.

There were no notable changes over time or differences between groups for vital signs, ECGs or laboratory values. No patient developed antibodies to atacicept, and atacicept treatment did not affect vaccine immunisation status.

Local tolerability

Of the patients who received atacicept, seven experienced local reactions: redness (four patients), tenderness (three patients), bruising (one patient) and swelling (one patient). All local reactions in the atacicept group were mild in severity. Local injection-site reactions were reported in two patients who received placebo: mild tenderness (two patients), moderate bruising (one patient) and mild redness (one patient). Local injection-site reactions in all patients resolved within 4 hours after injection. No notable difference in the incidence of local injection-site reactions was seen between atacicept dose groups. Pain scores were low in all groups: the maximum pain score was 15 (out of a possible 100) in the placebo group and 8 in the atacicept groups. In all but two cases, injection-site pain resolved within 30 minutes after injection.

PK

Maximum free atacicept concentrations were achieved at a median of 0.25–0.5 hours post-dose in all cohorts, corresponding to the first two PK sampling points (Table 3 and Figure 2). Free and total atacicept concentration–time profiles displayed multi-phasic

Table 2 Treatment-emergent adverse events reported during the study (the observation period was 6 weeks for single-dose cohorts and 9 weeks for the repeat-dose cohort)

Patient Event[a] *(events),* n	*Placebo* (n = *4*)	*Atacicept 3 mg/kg* (n = *5*)	*Atacicept 9 mg/kg* (n = *5*)	*Atacicept 18 mg/kg* (n = *5*)	*2 × 9 mg/kg Atacicept* (n = *5*)	*All* (n = *24*)
Total	1 (3)	3 (5)	1 (1)	1 (1)	4 (5)	10 (15)
Virus respiratory tract infection		2 (2)				2 (2)
Subcutaneous abscess					1 (1)	1 (1)
Upper respiratory tract infection				1 (1)		1 (1)
WBC count decreased					2 (3)	2 (3)
Constipation	1 (1)					1 (1)
Gastrointestinal motility disorder	1 (1)					1 (1)
Gastroesophageal reflux disease	1 (1)					1 (1)
Blepharitis allergic		1 (1)				1 (1)
Conjunctivitis allergic		1 (1)				1 (1)
Pyrexia			1 (1)			1 (1)
Headache					1 (1)	1 (1)
Eczema		1 (1)				1 (1)

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; WBC: white blood cell.
[a]Events listed by MedDRA-preferred term.

Table 3 Pharmacokinetic values[a] for free atacicept in patients who received active treatment

	Atacicept 3 mg/kg (n = 5)	*Atacicept 9 mg/kg* (n = 5)	*Atacicept 18 mg/kg* (n = 5)	*Atacicept 2 × 9 mg/kg first dose* (n = 5)	*Atacicept 2 × 9 mg/kg second dose* (n = 5)
$t_{1/2}$, h	642 (496–1000)	765 (489–880)	702 (638–1050)	102 (85.7–121)	710 (659–847)
t_{max}, h	0.50 (0.50–0.50)	0.25 (0.25–0.50)	0.50 (0.25–0.50)	0.50 (0.25–4.0)	504.25[b] (504.25–504.25)
C_{max}, mg/L	38.6 (32.4–46.4)	91.7 (70.7–641)	257 (214–448)	148 (104–160)	118 (83.2–132)
AUC_{inf}, mg h/L	953 (609–1130)	1770 (1450–2940)	4880 (4200–6090)	2650 (2580–3080)	4700 (2820–5170)
CL, L/h	0.282 (0.201–0.315)	0.319 (0.229–0.421)	0.287 (0.237–0.316)	0.223 (0.177–0.338)	—

Abbreviations: AUC_{inf}: area under the concentration–time curve extrapolated to infinity; CL: clearance; C_{max}: peak plasma concentrations; t_{max}: time to peak concentrations; $t_{½}$: elimination half-life.
[a]Data are presented as median (range).
[b]Last dose administered at 504 hours.

behaviour. This comprised at least two distribution phases, which occurred within 14 days post-dose, and a prolonged terminal phase characterised by median terminal half-lives of 642–765 hours for free atacicept (27–32 days) and 1100–2050 hours for total atacicept (46–85 days). The distribution phases appear to represent both the distribution of atacicept across tissues and binding of the drug to its ligands.

Serum levels of atacicept•BLyS complex showed a saturated (less than dose-proportional) increase across the doses studied (Figure 3). The evidence of non-linearity was weaker for free and total atacicept. The latter can be attributed to the diminishing influence of the binding non-linearity with the dose escalation. Despite the existing non-linearities, the PK of atacicept was very consistent and predictable across the doses and between single and repeat doses for all three variables.

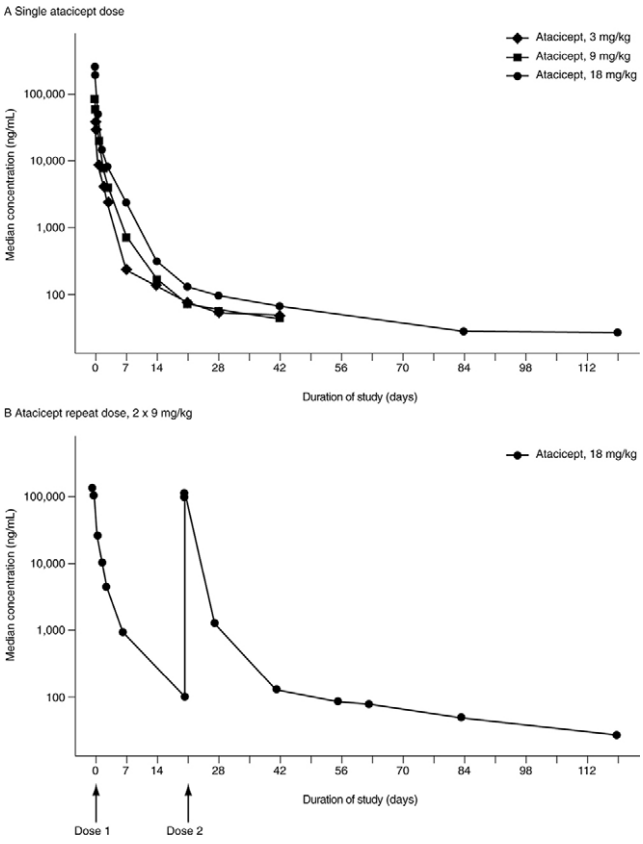

Figure 2 Free atacicept serum concentration versus time profiles after administration of (A) a single intravenous dose or (B) multiple intravenous doses of atacicept.

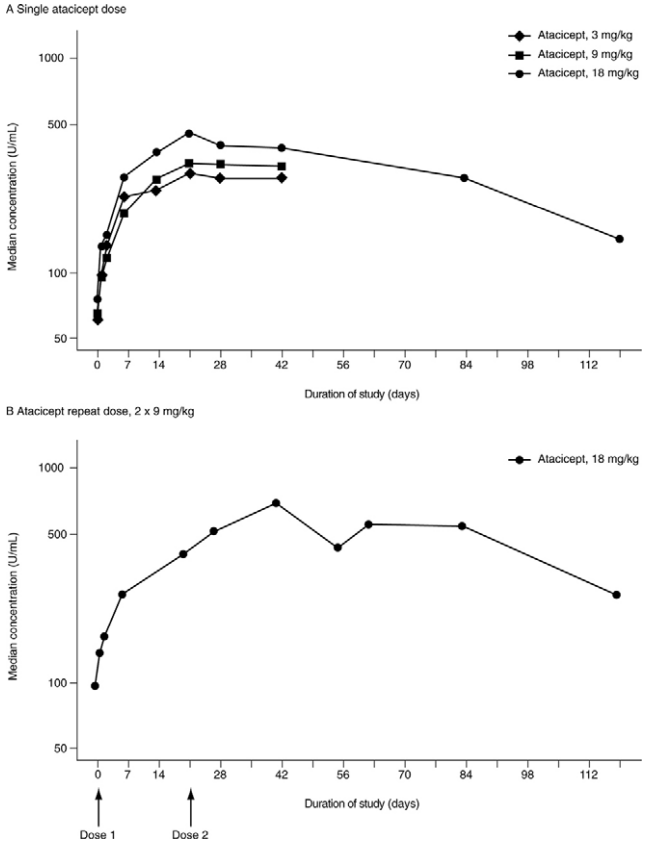

Figure 3 B-lymphocyte stimulator (BLyS) • atacicept complex serum concentration versus time profiles after administration of (A) a single intravenous dose or (B) multiple intravenous doses of atacicept.

The study design, involving a maximum of two doses administered over a 3 -week interval, did not permit any conclusions to be made about accumulation of atacicept in the body.

PD

Atacicept induced an initial transient increase followed by a dose-dependent reduction in mature and total B-cells (Figure 4A and B). The greatest reductions were seen in mature B-cells 6 weeks after a single dose in the 9 mg/kg group (40% reduction from baseline) and 7 weeks after the repeated dose in the 2 × 9 mg/kg group (55% reduction from baseline). Recovery of total and mature B-cell counts from the reduction phase was not seen during the relatively short course of the study. An initial transient increase was also observed in memory and naïve B-cells, with a subsequent recovery toward baseline. No notable drug-dependent changes were observed for T-cells (total, helper or cytotoxic), NK-cells or monocytes.

Ig levels decreased rapidly after atacicept dosing, with the greatest reductions seen for IgM (Figure 4C and D). The largest effect was seen in the 2 × 9 mg/kg group, which showed a median decrease from baseline of ~40% for IgM 6 weeks after the last dose (33% decrease in IgA, 20% decrease in IgG). In some treatment groups, decreases in IgM and IgA were preceded by transient increases of 5–10% from baseline. Comparison of results from the 18 mg/kg and 2 × 9 mg/kg groups at 4 weeks post-dose suggested a greater response with administration of the same total dose as two injections.

C3 levels remained within the normal range throughout the study for most patients. At baseline, only three of 24 patients had C3 values below the normal range (0.9–1.8 g/L): one patient in the 9 mg/kg group, one patient in the 18 mg/kg group and one patient in the 2 × 9 mg/kg group. All three of these patients showed transient increases in C3 to normal levels during treatment.

Anti-dsDNA antibody titres were negative at baseline for all except one patient. Therefore, no

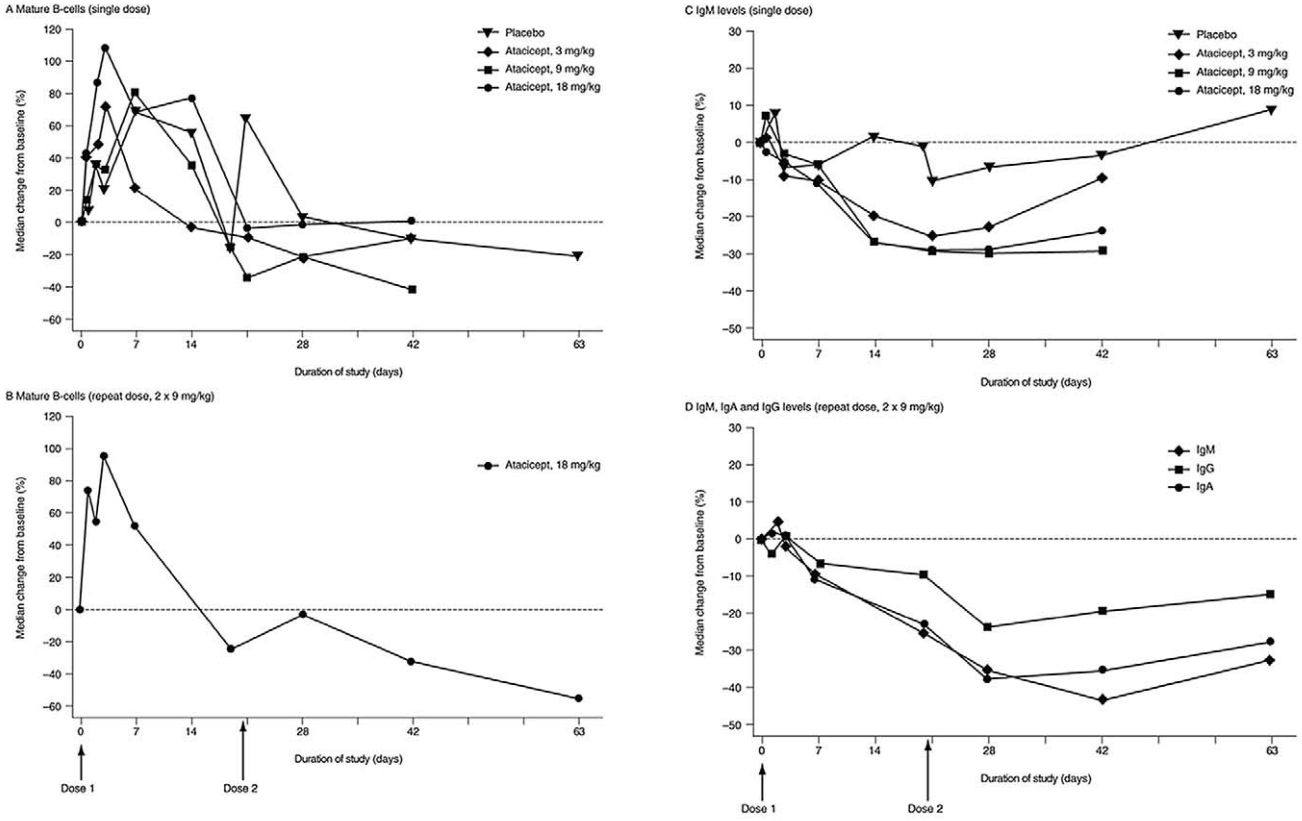

Figure 4 Median percentage change from baseline in (A) mature B-cell counts for single doses, (B) mature B-cell counts for a repeat dose, (C) immunoglobulin M (IgM) levels for single doses and (D) IgM, IgA and IgG levels after repeat doses, after intravenous administration of atacicept.

conclusions can be drawn about the effects of atacicept i.v. on autoantibody levels.

Discussion

We conducted a study to investigate the safety of single and multiple i.v. injections of atacicept in patients with SLE. Results showed that atacicept was well tolerated by patients with SLE, both systemically and locally, at a total dose of up to 18 mg/kg (as either a single dose or 2 × 9 mg/kg injections). Few AEs were observed and they were mild or moderate in severity. Decreased WBC counts occurred in two patients from the 2 × 9 mg/kg atacicept dose cohort. However, both patients had low WBC counts at baseline, and no significant decreases in WBC count were observed in the other patients in the study. Nevertheless, the number of patients is too small to draw any conclusions with respect to the use of multiple i.v. doses of atacicept in patients with pre-existing leucopenia. Local tolerability of atacicept was good with only transient, mild injection-site reactions reported. Overall, our results confirmed the favourable safety profile of atacicept that was observed previously with subcutaneous administration in healthy volunteers and in patients with rheumatoid arthritis.[31,32] Notably, there did not appear to be any safety concerns associated with concomitant administration of atacicept and medications commonly used in the management of SLE.

The PK profile of atacicept was non-linear but was predictable across doses and between single and repeat doses. Maximum free atacicept concentrations were achieved at a median of 0.25–0.5 hours post-dose. The slight delay in the maximum (relative to the instantaneous input assumption related to i.v. administration) is probably due to initial mixing into the central compartment.

Treatment with atacicept resulted in a reduction of B-cells and Ig levels in patients with SLE indicating biological activity consistent with its MoA. Specifically, reductions in mature B-cell counts and decreases in Ig levels are consistent with inhibition of BLyS and APRIL activity. Overall, PD effects were most marked in the 2 × 9 mg/kg group. This group showed a 55% reduction from baseline in mature B-cells 7 weeks after the second dose. In this study, we also observed marked reductions in IgM (–40%), IgA (–33%) and IgG (–20%) in the 2 × 9 mg/kg group 6 weeks after repeat dosing. Taken together, these data show that atacicept has a potent effect on B-cells and Ig levels in patients with SLE. These findings are consistent with those of a recent study of subcutaneously administered atacicept in patients with SLE that demonstrated sustained reductions in total and mature B-cells and in Ig levels at all doses, which were particularly marked in the repeat-dose groups.[35] This supports the utility of this therapeutic approach in the treatment of autoimmune diseases such as SLE.

Atacicept is one of a number of agents designed specifically to target B-cells in patients with SLE.[9,13] Rituximab, epratuzumab, atacicept and belimumab are all at various stages of clinical development for SLE. All of these agents bind to B-cell surface molecules, but affect B-cell activity in different ways. The monoclonal antibodies rituximab and epratuzumab bind to CD20 and CD22 cell-surface antigens, respectively, causing B-cell death,[36,37] whereas atacicept and belimumab (anti-BLyS monoclonal antibodies) prevent ligands from binding to cell-surface receptors, inhibiting B-cell growth and development, and reducing Ig production.[30,38] These differential MoAs are likely to result in different benefit-to-risk profiles for each agent. For example, the ability of atacicept to bind to both BLyS and APRIL may lead to a greater efficacy compared with belimumab, which binds only to BLyS.[38] Safety profiles may also differ according to the mechanism by which B-cell activity is reduced. While rituximab and epratuzumab may increase the risk of AEs associated with B-cell depletion, this may not be the case for atacicept and belimumab, which reduce B-cell activity but have a less profound effect on B-cell numbers. With this in mind, it is encouraging that none of the infection-related events we report here were considered to be related to atacicept and that atacicept did not compromise vaccine immunisation status.

In conclusion, i.v. atacicept was well tolerated, both systemically and locally, in patients with mild-to-moderate SLE at the doses investigated and demonstrated clear biological activity consistent with its predicted MoA. PK and PD results from this study will aid dose selection in larger studies that will further investigate the safety and efficacy of atacicept in patients with SLE.

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Conflict of interest statement

CRP and HS are employees of Merck Serono S.A. (Geneva, Switzerland). At the time of the study, JH and IN were employees of ZymoGenetics Inc. (Seattle, WA, USA).

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