B cells and B cell directed therapies in rheumatoid arthritis: towards personalized medicine
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ATACICEPT IN PATIENTS WITH RHEUMATOID ARTHRITIS. RESULTS OF A MULTICENTER, PHASE IB, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-ESCALATING, SINGLE- AND REPEATED-DOSE STUDY
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Abstract

OBJECTIVE. Atacicept is a recombinant fusion protein that binds and neutralizes B lymphocyte stimulator and a proliferation-inducing ligand. The purpose of this study was to investigate the tolerability, pharmacokinetics, and pharmacodynamics of atacicept treatment in patients with rheumatoid arthritis (RA) and to collect exploratory data on clinical outcomes.

METHODS. In this multicenter, phase Ib, randomized, placebo-controlled, dose-escalating trial, 73 patients were enrolled into 6 escalating-dose cohorts. Patients received atacicept or placebo as single doses (70, 210, or 630 mg) or as repeated doses given at 2-week intervals (3 doses of 70 mg, 3 doses of 210 mg, or 7 doses of 420 mg), followed by 10 weeks of trial assessments, with a followup assessment at 3 months after the final dose.

RESULTS. Atacicept was well tolerated, with few differences between treatment groups and no obvious safety concerns. The pharmacokinetics profile was nonlinear, but was consistent and predictable across all doses and regimens. Treatment-related decreases in immunoglobulin (particularly IgM) and rheumatoid factor levels were evident, and a clear decrease in anti-citrullinated protein antibodies was observed in the cohort that received 7 doses of 420 mg. The B cell response was biphasic, with an initial transient increase (dominated by memory B cells) followed by a dose related decrease (dominated by mature B cells). Clinical assessments showed trends toward improvement with the 3-month treatment. Little effect on the erythrocyte sedimentation rate or C-reactive protein levels was seen.

CONCLUSION. Atacicept was well tolerated both systemically and locally. The results demonstrated that the biologic activity of atacicept was consistent with its mechanism of action.

Introduction

Rheumatoid arthritis (RA) is a chronic syndrome characterized by nonspecific, usually symmetric, inflammation of the peripheral joints. Although the introduction of earlier aggressive treatment with disease modifying antirheumatic drugs (DMARDs) has played a major role in improving many patient outcomes, RA is still associated with long-term morbidity and early mortality.

The role of T cells in the pathogenesis of RA is well established, while that of B cells is not as well understood. B cells could potentially act as antigen presenting cells, secreting proinflammatory cytokines, producing autoantibodies, and activating T cells, which then infiltrate synovial tissue. The production of rheumatoid factors (RFs; antibodies that bind immunoglobulin) and anti-citrullinated protein antibodies (ACPAs) is among the characteristic
features of RA. These autoantibodies are generally thought to be associated with disease severity and prognosis \(^7\), although the association with ACPAs is a more controversial subject. Other autoantibodies detectable in the serum or synovial fluid of patients with RA include antinuclear factors, antineutrophil cytoplasmatic antibodies, and antibodies to native type II collagen, citrullinated peptides, and gp130-RAPS, the RA antigenic peptide-bearing soluble form of gp130. The relevance of autoantibody-producing autoreactive B cells in RA has been highlighted by the success of therapeutic B cell depletion \(^1\). Although the precise consequences of the decrease in the production of RFs and other autoantibodies are unknown, it has been proposed that small immune complexes containing RFs may activate macrophages in the synovial membrane via the Fcγ receptor \(^9\). These findings suggest that B cells are an appropriate therapeutic target.

Atacicept is a recombinant fusion protein that binds and neutralizes the activity of B lymphocyte stimulator (BLyS; trademark of Human Genome Sciences, Rockville, MD), a cytokine shown to be a key regulator of B cell maturation, proliferation, and survival, and APRIL, a proliferation-inducing ligand, which is another tumor necrosis factor (TNF) family member that is closely related to BLyS \(^1\). BLyS and APRIL are produced by a wide variety of cell types, and act on B cells to enhance survival, proliferation, antigen presentation, and class-switch recombination at various stages of B cell development \(^1\). Three TNF receptor–related receptors have been identified that have unique binding affinities for BLyS and APRIL: TACI, BCMA, and BAFF receptor (BAFFR). TACI and BCMA bind both BLyS and APRIL, while BAFF-R appears to bind only BLyS with high affinity \(^1\). APRIL also binds, with as yet unknown consequences, to heparan sulfate proteoglycans, such as syndecan 1/CD138 \(^1\).

Atacicept contains the BLyS/APRIL-binding extracellular portion of the TACI molecule fused to the Fc portion of human IgG1 and can be used to neutralize BLyS and APRIL and prevent them from binding to their receptors on B lymphocytes. Decreasing the levels of BLyS and APRIL in vivo is expected to result in a decrease in circulating mature B cells and Ig-secreting cells, and a consequent drop in Ig levels.

An important role of BLyS in the pathogenesis of autoimmune disorders is supported by the observation that transgenic mice expressing high levels of BLyS exhibit immune cell disorders and display symptoms similar to those in patients with systemic lupus erythematosus (SLE) and Sjögren’s syndrome \(^1\). In addition, serum levels of BLyS and APRIL are, on average, elevated in patients with RA and SLE \(^1\), although there is considerable overlap in the observed ranges of the serum concentrations of BLyS and APRIL in, for example, patients with RA as compared with healthy controls. Of interest, the levels of both BLyS and APRIL are higher in RA synovial fluid than in blood, particularly in the presence of significant joint inflammation, which suggests that these ligands may play an important role in the inflamed synovial compartment \(^1\).

In addition to elevated levels of BLyS and APRIL homotrimers, circulating heterotrimeric complexes of BLyS and APRIL have also been shown to be elevated in serum from patients with systemic immune–based rheumatic diseases (including SLE, RA, Reiter’s syndrome, psoriatic arthritis, polymyositis, and ankylosing spondylitis), and have been shown to induce B cell proliferation in vitro \(^1\). Among Ig fusion proteins for TACI, BCMA, and BAFF-R, only atacicept can block the biologic activity of all of these complexes \(^1\) and may have therapeutic utility in limiting the extent of tissue damage in RA.

Therefore, we conducted a phase Ib, randomized, double-blind, placebo-controlled, escalating-dose study at 7 clinical centers in Australia, The Netherlands, Russia, the former state of Serbia and Montenegro, and the UK to evaluate single and multiple doses of atacicept administered over 1 month and 3 months to patients with RA.
PATIENTS AND METHODS

The study (Merck Serono study code 25072) was conducted in compliance with the Declaration of Helsinki (2000 version) and with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. Approval was obtained from the Local Ethics Committees before study initiation, and written informed consent was obtained from all patients before performing any study procedures.

STUDY OBJECTIVES. The primary objective was to assess the systemic and local tolerability of single and repeated subcutaneous doses of atacicept in patients with RA. Secondary objectives were to assess the pharmacokinetics and pharmacodynamics of atacicept in patients with RA following single and repeated subcutaneous doses, to characterize biomarkers specific to the mechanism of action of atacicept and to document markers of disease activity and progression.

STUDY DESIGN. A total of 73 RF-positive patients with RA were included in the study and were grouped into 6 escalating-dose cohorts. Within each cohort, patients were randomized 3:1 to receive subcutaneous atacicept or placebo as single doses (70, 210, or 630 mg) or as multiple doses administered at 2-week intervals (3 doses of 70 mg, 3 doses of 210 mg, or 7 doses of 420 mg) (Figure 1). Dose escalation was authorized by a Safety Review Board upon review of the safety data. Predetermined dosing intervals for multiple doses were confirmed by a Pharmacokinetics/Pharmacodynamics Review Board, based on the results of pharmacokinetics and pharmacodynamics analyses in earlier cohorts.

Trial assessments were performed at baseline and continued for 10 weeks following administration of study drug, with a followup assessment at 3 months after the final dose.

PATIENT POPULATION. Adults of either sex who had active moderate-to-severe RA, which was defined as ≥6 swollen joints, ≥6 tender joints, and a C-reactive protein (CRP) concentration >15 mg/liter or an erythrocyte sedimentation rate (ESR) ≥28 mm/hour, were recruited. The main inclusion criteria were a disease duration of at least 6 months, failure of treatment with ≥5 DMARDs, RF positivity, and willingness to avoid pregnancy during the study and for 3 months after the last administration of study drug.

The primary exclusion criteria included any previous treatment with rituximab (anti-CD20 antibody) or anti-BLyS antibody, use of other biologic agents within 3 months before study day 1; prednisone dosage >10 mg/day or methotrexate dosage >17.5 mg/week; use of DMARDs other than methotrexate within 28 days before study day 1; history of, or prophylactic treatment for, tuberculosis; and significant concomitant illness or organ dysfunction.

PROCEDURES. Following randomization and baseline assessments, the first dose of study drug was administered subcutaneously into the anterior abdominal wall of each patient on study day 1. To protect blinding, the medication was administered by a nurse who was otherwise uninvolved in the study. Postdose blood and urine samples were collected for assessment of the pharmacokinetics, pharmacodynamics, safety, and disease activity. Samples were obtained at predefined intervals up to 14 weeks postdose (single-dose cohorts), 18 weeks postdose (repeat-dose cohorts 2 and 4), and 26 weeks postdose (repeat-dose cohort 6), with a followup assessment 3 months after the final dose (Figure 1).

OUTCOME MEASURES. Safety and tolerability assessments included physical examination, vital signs, electrocardiograms (EKGs), laboratory analyses (hematology, coagulation, clinical chemistry, and urinalysis), adverse events, and injection-site reactions. Assays for binding antibodies to atacicept were performed at baseline and the final followup assessment. Assays for neutralizing antibodies were performed if binding antibodies were detected. Antibodies titers to tetanus toxoid and diphtheria toxoid were compared between baseline and the final followup assessment to determine vaccine immunization status.

The following pharmacokinetics variables were measured using enzyme-linked immunosorbent assays (ELISAs): free atacicept, atacicept–BLyS complex, and composite atacicept (free atacicept plus atacicept–BLyS complex) and composite atacicept (free atacicept plus atacicept–BLyS complex/molar ratio). The atacicept–BLyS complex, and composite atacicept were assessed at 450 nm.

BLyS levels were measured by ELISA. For this purpose, biotinylated monoclonal antibodies to biotin-conjugated mouse monoclonal antibodies specific for BLyS (ZymoGenetics, Seattle, WA), goat polyclonal antibodies specific for biotin-conjugated BLyS (R&D Systems, Wiesbaden, Germany), or goat polyclonal antibodies to biotin-conjugated TACI-Ig (R&D Systems) were incubated with 1:10 dilutions of patient samples, standard, or control samples for 1 hour in streptavidin-precoated microplates. After washing, HRP-conjugated anti-BLyS mouse monoclonal antibody (ZymoGenetics) was incubated at room temperature for 1 hour. After washing, TMB was added as HRP substrate, the reaction was stopped after 20 minutes by the addition of 0.5 M sulfuric acid, and the absorbance was read at 450 nm. The analyte concentration of patient samples was recalculated using a standard curve, applying a polynomial second-order–fitting algorithm. All samples were measured in triplicate. As assay performance criteria, a precision of <15% for the coefficient of variation (CV) in the standard samples and >20% in the patient samples were accepted. The lower limits of quantification of the assays were 31.2 ng/ml of serum for free atacicept, 10 units/ml of serum for atacicept–BLyS complex (1 unit/ml corresponding to 1.82 ng/ml of atacicept to 0.44 ng/ml of BLyS in a 3:1 molar ratio), and 50 ng/ml of serum for the composite analytes. The mean spiking recoveries performed to test the accuracy for low, medium, and high analyte concentrations in RA patient samples corresponded to 82.5–97.0%, 93.9%, and 102.0–125.8% recovery rates, respectively, in the 3 assays.

The analyte concentration in patient samples was recalculated using a standard curve, applying a polynomial second-order–fitting algorithm. All samples were measured in triplicate. As assay performance criteria, a precision of <20% for the coefficient of variation (CV) in the standard samples and >20% in the patient samples was accepted. The lower limit of quantification was 1.56 ng/ml of BLyS in the serum. The mean spiking recoveries for low, medium, and high
concentrations of the analytes in RA patient samples corresponded to 101–113% recovery rates.

IgG (and IgG1–4 subclasses), IgM, IgA, ACPAs, and RFs (IgA, IgM, and IgG) were assessed in blood samples as markers of biologic activity, using conventional laboratory tests. A panel of cell types (B and T cell subsets, natural killer [NK] cells, and monocytes) was assessed in antibody-stained peripheral blood samples by 4-color flow cytometry. A contract research organization (Esoterix, Groningen, The Netherlands) performed blood sample processing, antibody staining, and acquisition, analysis, and quality control of the data. Serum CRP levels, ESRs, and urinary hydroxylysylpyridinoline (HP): lysylpyridinoline (LP) ratios were also measured as disease activity markers.

Disease assessments included the Disease Activity Score 28-joint assessment (DAS28) (22), tender and swollen joint counts (in 28 joints), patient’s assessment of pain (using a 0–100-mm visual analog scale [VAS]), physician’s global assessment of disease activity (using a Likert scale), patient’s global assessment of disease activity (using a 0–100-mm VAS), patient’s assessment of physical function (using the Health Assessment Questionnaire [HAQ]), and the duration of morning stiffness. Achievement of the American College of Rheumatology 20% improvement criteria (ACR20) 23 was assessed based on these data.

STATISTICAL ANALYSIS. The required sample size was determined so that the total numbers of patients would allow for the initial assessment of systemic and local tolerability as well as the pharmacokinetic and pharmacodynamic properties of atacicept. The safety analysis set was defined as all patients who received at least 1 injection of investigational treatment (analyzed as treated patients). The intent-to-treat analysis set was defined as all patients who were randomized. The 2 populations ended up being identical. Given the study’s safety focus and the small number of patients per cohort, only descriptive statistics and graphic representations were used. Continuous efficacy parameters were summarized over time, using actual values and percentages of change from baseline. Categorical parameters were summarized over time, using only frequencies and percentages. Imputation of missing values was used only for disease progression outcomes, and only in cases of study withdrawal due to disease progression. For binary variables (withdrawal due to disease progression), missing values were set at “no response” after withdrawal. For continuous variables, missing values were left missing. Treatment-emergent adverse events and features of the medical history were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 8.0). Past and concomitant medications were coded using the WHO Drug Dictionary (Quarter 1, 2004). Pharmacokinetics and pharmacodynamics were assessed through noncompartmental analysis, using WinNonlin Professional software, version 5.0.1 (Pharsight, Mountain View, CA).

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION.

Patients were enrolled from the former state of Serbia and Montenegro (n = 35), Russia (n = 29), The Netherlands (n = 7), Australia (n = 1), and the UK (n = 1). Overall, 73 patients were randomized and received treatment: 18 patients received placebo (combined placebo group), 6 patients each in the 3 single-dose cohorts received atacicept (cohorts 1, 3, and 5; 1 dose of 70 mg, 1 dose of 210 mg, and 1 dose of 630 mg, respectively), 9 patients each in cohorts 2 and 4 received atacicept (3 doses of 70 mg and 3 doses of 210 mg, respectively), and 19 patients in cohort 6 received atacicept (7 doses of 420 mg) (Figure 1).

Baseline characteristics were reasonably well balanced across treatment groups, considering the small numbers of patients. Overall, the mean ± SD age at study inclusion was 56 ± 8 years, and the mean ± SD disease duration at study inclusion was 7.9 ± 6 years. The majority of patients were female (81%). The mean ± SD body weight was 75 ± 14 kg. A history of smoking was reported by 34% of patients. All patients were RF+, as required by the protocol. The overall mean ± SD scores for the disease
activity measures were as follows: CRP 24 ± 29 mg/liter, ESR 46 ± 22 mm/hour, tender and swollen joint counts 16.1 ± 6.6 and 12.0 ± 4, respectively (28 joints assessed), pain (by VAS) 5.4 ± 1.8, patient’s global assessment of disease activity (by VAS) 5.7 ± 1.5, DAS28 6.6 ± 0.8, and HAQ score 1.7 ± 0.6. Concomitant treatments included methotrexate in 67% of patients and glucocorticoids in 48% of 64 patients. The mean ± SD level of BLyS at baseline was 2.33 ± 0.99 ng/ml.

All patients completed the study except 1; this patient (in cohort 1) withdrew because of disease progression after receiving a single, low dose of atacicept. Five patients discontinued treatment prematurely but completed all study observations. These discontinuations were because of generalized urticaria (1 patient in cohort 2 receiving atacicept), suspected erythema nodosum (1 patient in cohort 2 receiving atacicept), exacerbation of RA (1 patient in cohort 6 receiving atacicept), or disease progression (1 patient in cohort 2 and 1 in cohort 6, both receiving atacicept).

FIGURE No.1

FIGURE 1. Study protocol, showing the 6 treatment cohorts. Followup periods in the 6 different cohorts were as follows: A = 6 weeks; B = 4–6 weeks; C = 8–10 weeks; D = 6–8 weeks; E = 10–12 weeks; and F = 12 weeks. An Internal Data Monitoring Committee meeting was also held at each of these individual time points. Solid circles are increased in size with increased individual doses.

TABLE No.1

Summary of safety data, by treatment group*  

<table>
<thead>
<tr>
<th></th>
<th>COMBINED PLACEBO (N=18)</th>
<th>Cohort 1 ATACICEPT (N=4)</th>
<th>Cohort 2 ATACICEPT (N=5)</th>
<th>Cohort 3 ATACICEPT (N=3)</th>
<th>Cohort 4 ATACICEPT (N=9)</th>
<th>Cohort 5 ATACICEPT (N=9)</th>
<th>Cohort 6 ATACICEPT (N=7)</th>
<th>OVERALL (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total adverse events:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients – n (%)</td>
<td>8 (44%)</td>
<td>4 (67%)</td>
<td>5 (56%)</td>
<td>3 (50%)</td>
<td>4 (44%)</td>
<td>2 (33%)</td>
<td>2 (33%)</td>
<td>32 (44%)</td>
</tr>
<tr>
<td>Events – n</td>
<td>17</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>26 (36%)</td>
</tr>
<tr>
<td><strong>Severity – events, n (%):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>13 (76%)</td>
<td>4 (80%)</td>
<td>5 (56%)</td>
<td>5 (56%)</td>
<td>5 (42%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>45 (60%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (24%)</td>
<td>1 (20%)</td>
<td>4 (44%)</td>
<td>4 (44%)</td>
<td>6 (50%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>32 (40%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8%)</td>
<td>0</td>
<td>2 (8%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Serious events – patients (events)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)*</td>
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<tr>
<td>Treatment discontinuation due to adverse events – patients (events)</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Most frequent events† – patients, n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (11%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>2 (11%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>2 (11%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>0</td>
<td>1 (17%)</td>
<td>0</td>
<td>2 (33%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (4%)</td>
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<tr>
<td>Anaemia</td>
<td>0</td>
<td>0</td>
<td>2 (33%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (11%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>MedDRA ‘infections and infestations’ – patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (17%)</td>
<td>2 (33%)</td>
<td>1 (11%)</td>
<td>2 (33%)</td>
<td>3 (33%)</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
<td>14 (19%)</td>
<td></td>
</tr>
<tr>
<td>MedDRA ‘skin and subcutaneous tissue disorders’ – patients, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>2 (22%)</td>
<td>1 (17%)</td>
<td>0</td>
<td>0</td>
<td>4 (21%)</td>
<td>7 (10%)</td>
<td></td>
</tr>
<tr>
<td>Local reactions – patients, n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (itching, swelling, erythema, bruising, and/or ‘other’†)</td>
<td>2 (11%)</td>
<td>0</td>
<td>3 (50%)</td>
<td>4 (66%)</td>
<td>3 (50%)</td>
<td>1 (17%)</td>
<td>11 (58%)</td>
<td>24 (33%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>0</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>1 (11%)</td>
<td>1 (17%)</td>
<td>7 (37%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Pain (VAS &gt;0)</td>
<td>2 (11%)</td>
<td>0</td>
<td>1 (11%)</td>
<td>3 (50%)</td>
<td>2 (22%)</td>
<td>1 (17%)</td>
<td>8 (42%)</td>
<td>17 (23%)</td>
</tr>
</tbody>
</table>

* See Patients and Methods for a description of the individual cohorts. MedDRA Medical Dictionary for Regulatory Activities; VAS = visual analog scale (range 0–100 mm). † Two further serious adverse events (an electrocardiogram suggestive of myocardial ischemia and a fractured arm) were reported in patients who withdrew before receiving any treatment. One serious adverse event (death from lung cancer) was reported 8 months after completion of treatment in a patient in cohort 4. ‡ Reported in >2 patients overall. § Other reactions consisted of stinging and pain (1 patient each).
All treated patients underwent final followup evaluations.

TOLERABILITY OF ATACICEPT.

Overall, 32 patients (44%) reported 80 treatment-emergent adverse events (Table 1). Only 3 of these events were considered severe (arthralgia in cohort 4 atacicept group, and a rheumatoid nodule and an RA exacerbation in cohort 6 atacicept group), and half were considered unrelated or unlikely to be related to the study medication. There was no notable difference in the frequency of infection-related adverse events between patients who received atacicept and those who received placebo or between the treatment groups (Table 1). No infection-related events were considered serious or severe.

Events reported by >2 patients were fatigue, nasopharyngitis, chronic pyelonephritis, anemia, and headache. Two of the 3 patients with chronic pyelonephritis had a history of the condition at baseline. One patient in cohort 3 experienced worsening of chronic pyelonephritis and bronchopneumonia (resolving following treatment with oral antibiotics), with onset of symptoms at 6 weeks and 8 weeks, respectively, after a single dose of atacicept. Both events were considered to be of moderate severity and possibly related to the study medication, despite the interval between symptom onset and study treatment. Notably, the patient’s white blood cell counts and immunoglobulin levels were within normal ranges throughout the trial.

One patient in cohort 3 experienced worsening of chronic pyelonephritis and bronchopneumonia (resolving following treatment with oral antibiotics), with onset of symptoms at 6 weeks and 8 weeks, respectively, after a single dose of atacicept. Both events were considered to be of moderate severity and possibly related to the study medication, despite the interval between symptom onset and study treatment. Notably, the patient’s white blood cell counts and immunoglobulin levels were within normal ranges throughout the trial.

Skin and subcutaneous tissue disorders (according to the MedDRA system) were more frequent in patients receiving atacicept. However, the small study population and the small number of reported events do not permit us to draw any conclusions about a causal relationship. Two patients (cohort 2 and cohort 6, both receiving atacicept) experienced urticaria 4–6 hours after a dose of study medication; 1 of them had a history of drug allergies. A third patient (cohort 6 receiving atacicept) experienced macular erythema and pruritus, and a fourth patient (cohort 6 receiving atacicept) had a rash. Only 1 of these 4 patients discontinued treatment; the remaining 3 did not experience recurrence of symptoms with subsequent doses. One serious adverse event was reported during the study: pneumothorax occurred in this patient (cohort 3 receiving atacicept), which was related to a bronchoscopy for investigation of an abnormality present at baseline.

One death was reported poststudy in a 60-year-old man (cohort 4 receiving atacicept). This patient had a 40-year history of smoking and died of lung cancer ~8 months after completing study treatment. Local injection site symptoms were reported in 24 of the 73 patients. The most frequent local reaction was mild-to-moderate erythema, which was reported in 15 patients (36 mild erythema events, 3 moderate erythema events). Mild itching, swelling, bruising, and other
symptoms (stinging and pain) were each reported 8 times overall. VAS pain scores ≥0 were reported by 17 patients, but the scores were generally low (median of 15 on the 0–100-mm scale).

Assessment of data from the hematology, biochemistry, urine, coagulation, vital signs, and EKG studies showed no trends over time and few notable differences between treatment groups. The results of these evaluations did not suggest any potential safety concerns.

No binding antibodies to atacicept were detected. There were no appreciable changes in the titers of antibodies to tetanus toxoid or diphtheria toxoid following atacicept treatment.

PHARMACOKINETICS OF ATACICEPT.

Atacicept displayed nonlinear pharmacokinetics, characterized by a greater than dose-proportional increase in free atacicept, along with a less than dose-proportional, saturated increase in exposure to atacicept–BLyS complex (Figure 2). The evidence for nonlinearity was weaker for exposure to composite atacicept (free atacicept plus atacicept–BLyS complex). This may be because the nonlinearities of the individual pharmacokinetics of free atacicept and atacicept–BLyS complex offset each other within the composite atacicept measurement.

The concentration–time profiles of free and composite atacicept displayed multiphasic pharmacokinetics, with fairly rapid absorption for this class of molecules (time to maximum concentration 24 hours after the first dose), rapid distribution phases that were complete by 7–14 days after administration, and a prolonged terminal phase (terminal half-life 600–1,500 hours [25–53 days]).

Very little, if any, accumulation of free atacicept was observed with multiple doses. The accumulation of composite atacicept was moderate, while the accumulation of atacicept–BLyS complex continued throughout the entire dosing period (up to 7 doses every 2 weeks in cohort 6). There were indications that a pseudo–steady state would be achieved shortly after the seventh dose in this cohort.

Despite their nonlinearity, the pharmacokinetics profiles of atacicept were very consistent and predictable across all doses and between single and multiple doses for all 3 variables (free atacicept, atacicept–BLyS complex, and composite atacicept).

Although the small number of patients who underwent synovial fluid sampling (n = 4) limits the conclusions that can be drawn, there was evidence that atacicept was detectable in inflamed joints. The levels of free atacicept and atacicept–BLyS complex in synovial fluid were approximately one-third and one-half the levels in serum, respectively. In these patients, the concentrations of BLyS in synovial fluid before atacicept administration were ~4 times higher than those measured in serum, as might have been predicted from the values reported in published studies (5,6).

PHARMACODYNAMICS OF ATACICEPT.

Immunoglobulins. Immunoglobulin values showed prompt decreases following the first dose of atacicept, which continued with repeated dosing. In atacicept-treated patients in cohort 6, maximum reductions were seen on day 85. IgG values were reduced by a median of 21%, IgA by 37%, and IgM by 54%, compared with baseline (Figure 3A). The median IgA values showed a dose-dependent decline; values on day 85 were below baseline in all cohorts. Most obviously in the 3-month cohort 6, IgA values returned toward baseline after treatment cessation; however, they had not yet reached prestudy levels by the final assessment (12 weeks after the final dose). For IgG, the median values were more variable, especially in the placebo and cohort 1 atacicept groups. Three months after a single or final dose, IgG values were generally at or near baseline levels. IgG subclasses (IgG1–4) showed decreases with treatment that were roughly parallel to those observed for the total IgG values. Treatment-related decreases were most evident for IgM. In the combined placebo group, median IgM values did not vary substantially from baseline levels during the observation period. In contrast, all atacicept groups showed a rapid decrease in IgM following the first dose, which...
was apparently dose-independent during weeks 1–2. Thereafter, the nadir was dose-related, with the largest response observed in the cohort 6 atacicept group. A greater reduction in IgM was observed with atacicept administered as 3 doses given over a month, as compared with administration of the same total dose as a single injection. In most treatment groups, IgM values had returned to near baseline levels by the end of the observation period; exceptions were the largest single dose (630 mg) and the longest treatment duration (7 doses of 420 mg).

Rheumatoid factors. Decreases in RFs were observed following atacicept administration, most consistently with 7 doses of 420 mg of atacicept, although baseline values differed considerably between groups, and the response in the placebo group was much more variable for the RFs than for the nonspecific immunoglobulins. In atacicept-treated patients in cohort 6, maximum decreases from baseline of 41–44% were observed for all 3 RF classes (Figure 3B). Particularly in cohort 6 patients receiving atacicept, RFs showed decreases consistently more often than were seen for nonspecific immunoglobulins.

Anti–citrullinated protein antibodies. Little change in the ACPA values and little difference between active treatment and placebo groups were noted for patients in cohorts 1 through 5. In cohort 6 patients receiving atacicept, ACPA levels consistently decreased, with a median percentage change from baseline of -25% on day 85, as compared with a 2.6% increase in patients receiving placebo (Figure 4).

Markers of inflammation and cartilage degradation. Up to 3 months of treatment with atacicept did not lead to any appreciable effects on the ESR, the CRP level, or the urinary HP:LP ratio. Slight overall decreases were observed, but these were difficult to interpret because there was high variability between patients for all 3 of these measures.

Findings of flow cytometry. Atacicept treatment produced a biphasic response in total B cells (CD19+), mature B cells (CD19+IgD+,CD27-), memory B cells (CD19+CD20+CD27+,CD38-), immature B cells (CD19+IgD-,CD27-), as well as naive B cells (CD19+CD20+CD27-,CD38-), which was not seen among patients who received placebo. The initial phase consisted of a transient dose-related increase in cell concentrations observed within 2 weeks after a single (or the first) dose. Memory B cells, which accounted for most of this response, displayed the highest median percentage change, and mature B cells displayed the lowest median percentage change in this first phase. The second phase consisted of a sustained, dose-related reduction of B cell concentrations to below predose levels, which was most evident in the median percentage change from baseline among mature and total B cells (maximum decrease

**FIGURE No.4**

![Summary profile of the median levels of anti–citrullinated protein antibodies (ACPAs) in placebo-treated and atacicept-treated patients in cohort 6. Horizontal line represents baseline.](image)

**FIGURE No.5**

![Median percentage change in absolute counts of total B cells and mature B cells compared with baseline. The number of total B cells (CD19+) in A, the single-dose cohorts and B, the repeated-dose cohorts, and the number of mature B cells (CD19+IgD+,CD27+) in C, the single-dose cohorts and D, the repeated-dose cohorts (based on absolute concentrations) are shown. Horizontal line represents baseline.](image)
30–40% at 3 months) (Figure 5). Mature B cells accounted for most of the reduction phase of the total B cell response in terms of the percentage change from baseline.

Flow cytometric analyses showed no drug-related effects on total, helper, or cytotoxic T cells, NK cells, or monocytes (data not shown). Pre–germinal center B cells, plasma cells, plasmablasts, and Ig–secretory cells were too sparse in the peripheral blood to allow meaningful interpretation.

This study was not powered to show statistically significant effects on clinical end points. However, pilot information on clinical outcomes was collected, including DAS28 scores and ACR20 responses. DAS28 scores indicated an improvement in RA signs and symptoms with atacicept treatment, particularly in cohort 6. The atacicept-treated patients in cohort 6 had a mean ± SD DAS28 score of 6.4 ± 1.3 at baseline, which had decreased to 5.1 ± 1.4 on day 85. The decrease persisted long beyond treatment cessation and had only slightly diminished by the followup visit. No change was seen in patients who received placebo.

During the 3 months of atacicept treatment, 6 of 19 patients (32%) attained an ACR20 response or better, 2 of whom attained an ACR70 response. Another 3 atacicept–treated patients (16%) attained an ACR20 response or better during the observational followup period, 1 of whom attained an ACR50 response. No responses were seen among the placebo-treated patients in cohort 6 at either time point, although ACR20 responses occurred among some placebo recipients in other cohorts.

Assessment of individual components of the ACR20 criteria for improvement showed some effect on the tender joint counts and possibly on the swollen joint counts at the end of the 3-month treatment period. Most of the effect on the ACR20 response came from the patient’s self-assessments of pain and overall disease activity. Patient-reported assessments showed improvements as early as 2 weeks after treatment initiation. No marked trend was evident for physical functioning, as assessed by the HAQ.

DISCUSSION

Atacicept was generally well tolerated both systemically and locally. Infections were carefully monitored in this trial, since depletion of B cells and immunoglobulins with atacicept therapy, as with any other B cell–targeted therapy, may put patients at risk. In this trial, there was no notable difference in the rates of “infections and infestations” (according to the Med-DRA system) between atacicept-treated and placebo-treated patients. Future controlled trials will carefully monitor patients for infections and identify the optimal dose of atacicept as a potential treatment of RA.

More atacicept–treated patients experienced skin and subcutaneous tissue disorders (2 cases of urticaria, 1 case of macular erythema and pruritus, and 1 case of rash). One of the patients who experienced urticaria had a history of allergy to medicinal products, which was discovered upon investigation of the adverse event in the study, and treatment was discontinued. The remaining 3 patients did not experience a recurrence of symptoms with subsequent doses of atacicept. Although the limitations of this study (phase Ib trial, with a small study population and short treatment duration) must be taken into account, no potential safety concerns were identified.

Atacicept displayed nonlinear pharmacokinetics, characterized by a more than dose-proportional increase in free drug and a less than dose-proportional, saturated increase in atacicept–BLyS complex. Concentration–time profiles of free and composite atacicept displayed multiphasic pharmacokinetics, with fairly rapid absorption for this class of molecules, rapid distribution phases, and a prolonged terminal phase. The distribution phases appear to represent both the “true” distribution across tissues and, for free atacicept, the binding of the drug to its ligands. Indeed, the proportion of the overall area under the curve that corresponds to the distribution phase appears to be much higher for free atacicept than for composite atacicept; this difference is presumably largely explained by the binding. Very little, if any, distribution was seen for the atacicept–BLyS complex.

Minimal accumulation of free atacicept was observed with multiple doses. The accumulation of composite atacicept was moderate, while the accumulation of atacicept–BLyS complex continued throughout the entire dosing period (up to 7 biweekly doses in cohort 6). There were indications that a pseudo–steady-state would be achieved shortly after the seventh dose in this cohort.

Overall, the pharmacokinetics profiles of atacicept were consistent and predictable across the study doses and between the single and multiple doses. The results support the hypothesis that the pharmacokinetics of atacicept is mediated by its ligands.

Changes in pharmacologic biomarkers were consistent with the proposed mechanism of action of atacicept. Immunoglobulins and other biomarkers showed prompt reductions following the first dose of atacicept, which continued and showed greater reductions with repeated dosing. The greatest effects were seen with the 7 doses of 420 mg regimen of atacicept treatment. Reductions peaked within a few days of the last dose,
after which levels returned toward baseline. This treatment effect was particularly evident for IgM.

There was a biphasic response in the numbers of total, mature, and immature B cells, comprising an initial increase within 2 weeks after a single (or the first) dose, followed by an approximately dosedependent reduction (maximum decreases 30–40% at 3 months). As expected from the preclinical findings, there were no drug-related effects on the numbers of total, helper, or cytotoxic T cells, NK cells, or monocytes. The results of these analyses indicate that concentrations of peripheral blood mature and total B cells are potentially useful markers of drug effects in patients with RA.

This study did not have sufficient power to evaluate clinical efficacy. However, positive trends were seen for effects on signs and symptoms of RA with 3-month atacicept treatment (DAS28 scores and ACR20 responses). Individual components of the ACR20 criteria for improvement showed some effect on the tender joint counts and perhaps on the swollen joint counts toward the end of the treatment period. However, ACR20 improvements were dominated by patient-assessed outcomes (pain, HAQ scores, and patient’s global assessment), which showed improvement after as little as 2 weeks of treatment, which was earlier than anticipated and was well before the maximal effect on pharmacodynamic markers was seen. The lack of a clear treatment effect on markers of inflammation (ESR, CRP levels, and tender and swollen joint counts) suggests that further study is necessary to understand the effect of atacicept on the pathology of RA and, specifically, whether a longer treatment period would demonstrate the anti-inflammatory effects in patients with RA and, specifically, whether a longer treatment period would demonstrate the anti-inflammatory effect of atacicept on the pathology of RA.

In summary, this exploratory phase Ib trial showed atacicept to be generally well tolerated both locally and systemically in patients with RA. Both the pharmacokinetics and pharmacodynamic profiles of atacicept were consistent with the proposed mechanism of action of the drug. These data will allow us to define dose ranges and regimens for the future trials that will be needed to characterize the safety profile of atacicept, enhance our understanding of its mechanism of action, and define its optimal clinical use.

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