Atacicept, a novel B cell-targeting biological therapy for the treatment of rheumatoid arthritis

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Main Document (includes tables and figure legends)

Running header: Atacicept in rheumatoid arthritis

Abstract

**Background:** Recent data suggest a key role for B cells in the pathogenesis of many autoimmune diseases including rheumatoid arthritis (RA), and biological therapies targeting B cells are promising treatments for patients with RA. Atacicept inhibits B cell maturation, differentiation and survival, and immunoglobulin production by depriving B cells of growth and development signals. Therefore, atacicept may represent an effective strategy in RA treatment.

**Objective:** To evaluate the potential value of atacicept in RA treatment based on preclinical and clinical studies.

**Methods:** Preclinical and clinical data on atacicept were identified using PubMed and systematically reviewed.

**Results/conclusion:** Preclinical and clinical studies show that atacicept is well tolerated, with no increased incidence of infections. Atacicept displays non-linear pharmacokinetics, with a more than dose-proportional increase in free drug and less than dose-proportional, saturated increase in atacicept–ligand complex. Overall, the pharmacokinetic profiles of atacicept were consistent, dose-related and predictable. Dose-dependent reductions in immunoglobulins and other biomarkers, including rheumatoid factor, occurred rapidly but returned to baseline after discontinuation. There was a biphasic response in B cell number, but no effect on other leucocytes. Atacicept improved the signs and symptoms of RA, although larger studies are needed to confirm its efficacy and its optimal use.
Keywords: atacicept; B cells; biological therapies; growth factors; rheumatoid arthritis
1. Introduction

Rheumatoid arthritis (RA) is characterised by chronic synovial inflammation, leading to pain and damage of the affected joints and cartilage. During the past 25 years, significant advances have been made in the treatment of RA. First-line treatment is usually with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), sulphasalazine and leflunomide [1], with introduction of tumour necrosis factor (TNF)-α blockade therapies if patients continue to have active disease. The introduction of TNF-α blockers represented a new era of targeted biological therapies. Unlike traditional DMARDs, which result in non-specific suppression of the immune system [2], biological therapies target specific molecules or cells based on our improved understanding of the pathogenesis of RA. However, in a proportion of patients with RA, TNF-α blockade fails to achieve a satisfactory clinical improvement or a sustained clinical response over time. Furthermore, the use of anti-TNF-α is associated with increased risk of infections [3, 4].

In this regard, although RA has been considered primarily a T cell-mediated disease, recent data support a key role for B cells [5, 6]. The success of B cell-depleting therapy with rituximab underscored further the importance of B cells in the pathogenesis of RA [7].

2. Review

2.1 Overview of the market

Rituximab was the first licensed B cell-depleting therapy for the treatment of RA. It was initially developed for the treatment of non-Hodgkin’s lymphoma (NHL) [8], but was found to be effective in several autoimmune disorders, including RA [9]. Rituximab is licensed for use in combination with methotrexate for the treatment of
adults with severe, active RA who have had an inadequate response to, or intolerance of, other DMARDs, including at least one TNF-α inhibitor [10]. Rituximab has proven efficacy in patients with RA refractory to TNF-α blockers, with approximately 50% of patients achieving at least a 20% improvement in American College of Rheumatology criteria (ACR20) [11, 12]. Complete remission after a single course of rituximab treatment is rare, however, and most patients experience disease relapse between 6 and 12 months, even when peripheral B cell number remains suppressed [13–17]. Re-treatment with rituximab may be effective and appears safe [18], but alternative treatments that target B cells may also be efficacious in this patient population. In this regard, several other B cell-targeting biological therapies have been developed. These include other monoclonal antibodies (mAbs) that target CD20 or other B cell-surface molecules (e.g. CD19 and CD22). An alternative approach to decreasing B cells is to target the B cell-activating factor, B lymphocyte stimulator (BLyS; also known as B cell-activating factor belonging to the tumour necrosis family (BAFF), TALL-1, zTNF4 and CD257) and the related cytokine APRIL (a proliferation-inducing ligand or CD256) by blocking the interactions between BLyS/APRIL and their receptors [19].

2.2 Introduction to the compound

Atacicept is a fully human, recombinant receptor–immunoglobulin (Ig) fusion protein. Biochemically, atacicept is a homodimeric fusion protein (molecular mass, 73.4 kDa [20]) containing the extracellular, BLyS/APRIL-binding domain of the TACI (transmembrane activator and calcium-modulating and cyclophilin-ligand interactor) molecule and the Fc portion of human IgG1. Atacicept binds to the B cell growth factors BLyS and APRIL (Figure 1) [21]. BLyS acts on B cells to enhance maturation,
proliferation, survival, antigen presentation and antibody class-switching at various stages of B cell development [22]. APRIL, a homologue of BLyS, has a similar action on B cells [23]. Both BLyS and APRIL are produced by a wide variety of cell types, and can form homotrimers as well as heterotrimers (Figure 2). BLyS and APRIL exert their biological function by signalling through their receptor proteins: TACI and BCMA (B cell-maturation antigen) receptors. BLyS also has a high affinity for BAFF receptors (BAFF-R), and APRIL can bind with low affinity to heparan–sulphate proteoglycans. TACI is a membrane receptor expressed on specific populations of B cells and on activated T cells. Indeed, it has been reported that BLyS can co-stimulate T cells under certain circumstances [24]. In B cells, TACI is expressed weakly on immature transitional type-1 B cells, and at high levels on immature transitional type-2 B cells, marginal-zone B cells and activated B cells, but not on germinal-centre (GC) B cells [24]. However, TACI expression is induced upon the differentiation of GC B cells into plasma cells [25].

The expression of B cell growth-factor receptors and CD20 on B cell subsets is summarised in Table 1. As a result of differential responsiveness of to BLyS and APRIL, atacicept inhibits the generation of autoreactive plasma cells that produce autoantibodies, but spares pro- and pre-B cells and some immature B cells [23]. In vitro, atacicept inhibits the proliferation and differentiation of naïve B cells and GC B cells, as well as the generation of plasma cells [25]. Furthermore, Benson et al. showed that simultaneous inhibition of BLyS and APRIL in mice is necessary for the decrease in plasma cells, but does not decrease memory B cells [29], although caution is needed when extrapolating these findings to the clinic. This decrease is reversible as there is a rapid recovery of B cell numbers upon discontinuation of atacicept [30]. Thus, atacicept acts as a competitive antagonist to BLyS and APRIL and represents a promising novel strategy in the
management of diseases characterised by B cell hyperactivity, such as RA, systemic lupus erythematosus (SLE) and B cell malignancies.

In many autoimmune rheumatic diseases, including RA, elevated levels of circulating BLyS/APRIL heterotrimers were detected in patient serum [31]. Furthermore, transgenic mice overexpressing BLyS exhibit a lupus-like syndrome and have high titres of anti-double-stranded DNA antibodies, rheumatoid factor (RF) and proteinuria, as well as Ig deposition in the kidneys and glomerulonephritis [32]. Half of these animals also have elevated serum Ig levels. These observations suggest that BLyS and APRIL may play an important role in the pathogenesis of RA and SLE, although their precise role remains under debate. For instance, Stol et al showed that serum APRIL levels inversely correlated with serum anti-dsDNA titres or disease activity in SLE [33], and APRIL may have both pro- and anti-inflammatory activities in RA [34]. Furthermore, the network that governs B cell survival is complex and has not been fully defined (reviewed in [35]). For instance, data from TACI knockout models suggest that TACI plays an inhibitory role in B cell development [36]. Therefore, targeting BLyS/APRIL by atacicept may not produce the anticipated effects.

To evaluate the potential use of atacicept in RA treatment based on available preclinical and clinical studies, published literature on atacicept and TACI-Ig fusion proteins in preclinical and clinical studies was identified using the PubMed database and systematically reviewed. The search was limited to literature published in English using the search terms atacicept, TACI-Ig and TACI plus Fc.

2.3 Pharmacodynamics (PD)

2.3.1 Preclinical data
Atacicept was shown to inhibit disease progression in a murine model of collagen-induced arthritis [23]. Naïve mice were treated with 100 µg of human TACI-Ig, human Ig or phosphate-buffered saline three times weekly for two weeks. Disease incidence and the severity of inflammation were lowered when atacicept was administered both before disease onset and after disease was established. Atacicept inhibited the production of collagen-specific antibodies and a decreased number of follicular B cells was observed in the spleen.

Data from the use of atacicept in other animal models have provided further valuable information on the pharmacodynamics of the drug. For instance, in a murine model of SLE, treatment with 20 or 100 µg of atacicept three times weekly for 5 weeks led to a significant reduction of proteinuria for up to 10 weeks [37]. The higher dose regimen also significantly increased the survival of animals, and this effect was correlated with a decrease in peripheral blood B cells (a 53% reduction compared with controls) and persisted for 5 weeks post-treatment. In another study, atacicept (0.4, 2 or 10 mg/kg) was administered to mice either as a single dose or as repeated doses on alternate days for 2, 4 and 26 weeks [30]. In the 26-week study, antibodies against atacicept were detected in animals treated at the lower doses but not the 10 mg/kg dose, and were associated with higher than expected levels of IgG and IgM.

2.3.2 Clinical data

2.3.2.1 Healthy volunteers

In a phase I, double-blind, dose-escalating, sequential-dose study, 23 healthy male volunteers received a single subcutaneous injection of 2.1, 70, 210 or 630 mg of atacicept or placebo and were followed up for 7 weeks [38]. A single dose of atacicept resulted in a dose-dependent reduction of serum IgM levels for up to 210 days post-
dose; the highest dose was associated with a 23% decrease in IgM levels 2 weeks after treatment [38]. There were no treatment-related effects on IgG levels or lymphocyte subpopulations. Biological effects were not apparent for placebo and the 2.1 mg atacicept dose. No other clinically significant changes in laboratory parameters or vital signs were observed in any treatment group.

2.3.2.2 RA patients

A phase Ib, randomised, double-blind, placebo-controlled, dose-escalating study was conducted in 73 RF-positive patients with active, moderate-to-severe RA [39, 40]. The patients were given atacicept or placebo as single doses (70, 210 or 630 mg) or as repeated doses (3 doses of 70 or 210 mg, or 7 doses of 420 mg) every fortnight. IgM, IgA and IgG levels fell rapidly in a dose-dependent manner after the first dose of atacicept, and continued to decrease with subsequent doses. In patients who received 7 × 420 mg of atacicept, IgM, IgA and IgG levels dropped by 54%, 37% and 21%, respectively from baseline (Table 2). The levels of all Ig isotypes began to recover at the end of the dosing regimen and were at, or close to, baseline values 12 weeks after the last dose. RF levels of all three classes were consistently reduced (between 41 and 44% of baseline) after 7 × 420 mg atacicept (Table 2) and returned to baseline levels within 2–3 months after the treatment discontinued. The levels of anti-cyclic citrullinated peptide (CCP) antibodies were unaffected except in patients receiving the maximum dose of atacicept, in whom levels were consistently decreased (Table 2). Atacicept treatment led to a biphasic response in the number of total and mature B cells, as well as memory, immature and naïve B cells, in the peripheral blood. The initial phase consisted of a transient dose-related increase in cell numbers, with memory B cells displaying the highest median percentage change, and mature B cells
the lowest. The second phase consisted of a sustained, dose-related reduction of B cells to below pre-dose levels. **No anti-atacicept antibodies were detected and no changes in vital signs were observed.**

### 2.4 Pharmacokinetics (PK)

#### 2.4.1 Healthy volunteers

In 23 healthy volunteers receiving a single subcutaneous injection of 2.1, 70, 210 or 630 mg of atacicept, serum levels of free drug were dose-dependent and reached their maximum at 16 hours post-injection [38]. BLyS–atacicept complex levels persisted longer, however, peaking between 14 and 35 days post-dose, and were measurable for up to 210 days. With increasing doses, increases in the maximum serum concentration and the area under the concentration–time curve were non-linear, indicating that there was a decrease in apparent clearance with increasing dose. These observations suggest that increasing the atacicept dose beyond the amount necessary for saturation would not lead to a significant increase in the atacicept–BLyS complex profiles and is thus unlikely to bring additional clinical benefit. The median terminal elimination half-life of atacicept was 12.4 days. The value was slightly higher in the higher-dose arms, which may be due in part to the sampling scheme and in part to the high proportion of terminal values below the lower limit of quantification in the lower-dose arms.

#### 2.4.2 RA patients

In the phase 1b study of 73 patients with RA, atacicept also displayed multiphasic PK with a greater than dose-proportional increase in free atacicept. Peak concentrations were reached approximately 24 hours after the first dose, followed by at least one distribution phase (complete by 7–14 days after administration) and a long terminal
elimination phase (terminal half-life of 25–63 days). There was a less than dose-
proportional, saturated increase in atacicept–BLyS complex. Accumulation of 
atacicept–BLyS complex continued throughout the entire dosing period. Atacicept 
was also detectable in two of four patients who underwent synovial fluid sampling, 
with levels similar to the measured serum concentrations in the same patient at the 
same time point. The PK profiles of atacicept were consistent and predictable across 
all doses and between single and multiple doses [39, 40]. The PK profile of atacicept 
7 × 420 mg after the first and last dose is shown in Table 3.

2.5 Clinical efficacy

2.5.1 Rheumatoid arthritis

In the phase 1b study, atacicept-treated patients in the 7 × 420 mg group had a mean 
Disease Activity Score using 28 joint counts (DAS28) of 6.4 at baseline, which 
improved to 5.1 on day 85 and persisted beyond treatment cessation [39]. No change 
was seen in patients who received placebo. During the 3 months of atacicept 
treatment, 32% of patients achieved an ACR20 response, with two achieving an 
ACR70 response. The effect on the ACR20 response occurred as early as 2 weeks 
after treatment initiation.

2.5.2 Ongoing clinical studies in RA

Given the positive results in the early studies, several phase II clinical trials are 
currently ongoing and include:

(i) Dose-finding study (ClinicalTrials.gov Identifier: NCT00430495)
This is a multicentre, randomised, double-blind, placebo-controlled study started in 2006, testing three dose levels of atacicept in 300 patients with RA who had inadequate responses to TNF-α blockers.

(ii) Combination study with rituximab (ClinicalTrials.gov Identifier: NCT00664521)

Two recent studies demonstrated that the serum levels of BLyS were significantly increased after treatment with rituximab [41, 42]. Furthermore, the serum levels of APRIL in patients with RA were found to be 10-fold higher than normal controls and remained elevated after treatment with rituximab. These observations indicated that atacicept may be a useful adjunct to rituximab therapy. Therefore, a phase II clinical trial was initiated to evaluate the safety and efficacy of combined treatment with atacicept and rituximab in patients with RA receiving treatment with rituximab.

(iii) Study in anti-TNF-α naïve patients with moderate-to-severe RA and an inadequate response to methotrexate (ClinicalTrials.gov Identifier: NCT00595413)

This is a phase II study investigating the efficacy of atacicept compared with placebo in the treatment of patients with RA with inadequate response to MTX and no previous exposure to anti-TNF-α therapy.

2.6 Safety and tolerability

2.6.1 Healthy volunteers

In the study of 23 healthy volunteers given a single subcutaneous dose of atacicept (at 2.1, 70, 210 or 630 mg) or placebo, the adverse events were similar between all groups [38]. Mild-to-moderate, transient adverse events were reported in 17 participants (73.9%); the most frequent events were headache, sore throat and head cold. There was no correlation between atacicept dose and any adverse event. Participants who had levels of atacicept–BLyS complex above baseline at week 7
entered an extension period, with PK/PD sampling at monthly intervals. No treatment-related adverse events were reported during the extension phase. During the main study and extension phase there were no deaths, no serious or life-threatening adverse events, no clinically significant changes in the measured safety parameters and no withdrawals relating to adverse events. Injection-site pain immediately after injection (assessed by 100 mm visual analogue scale [VAS]) was reported by 16 participants. The highest VAS scores for pain were observed in participants in the 210 mg and 630 mg groups. The higher doses were also more likely to be associated with mild, acute or prolonged injection-site redness, which was probably related to the greater injection volumes and number of injections.

2.6.2 Rheumatoid arthritis

In the phase Ib clinical trial of 73 patients with RA [39], atacicept was found to be well tolerated. Adverse events were reported by 32 patients (44%); only three events were considered to be severe (arthralgia in the 3 × 210 mg cohort; rheumatoid nodule and an RA exacerbation in the 7 × 420 mg cohort). There was no significant difference in the frequency of infection-related events between patients who received atacicept and those who received placebo, or between treatment groups. No infection-related events were considered serious or severe. One serious adverse event (pneumothorax) and one death (lung cancer) occurred during the study; neither was considered to be related to treatment. Local injection-site symptoms were reported in 24 patients, the most frequent being mild-to-moderate erythema (15 patients). VAS pain scores >0 were reported by 17 patients (median, 15 mm).

2.6.3 Other conditions
Atacicept has been investigated in a number of other conditions, including SLE, NHL and multiple myeloma. These studies provide valuable additional clinical data on the safety and tolerability of atacicept. In a phase Ib study, 47 patients with mild-to-moderate SLE received either single doses of atacicept (0.3, 1, 3 or 9 mg/kg), or weekly doses of atacicept (1 or 3 mg/kg) or placebo, for 4 weeks [43]. There were no statistical differences in the frequency or type of adverse events, including infections, between the placebo and atacicept groups. Adverse events were reported by 78% of patients in the single-dose cohorts and by 77% of patients in the repeated-dose cohorts. All events were mild or moderate in severity, except for an event of severe paraesthesia in a patient receiving repeated-dose placebo. There were no withdrawals or discontinuations related to adverse events, and no serious adverse events in patients receiving atacicept. Injection-site redness was observed in 50% of all patients receiving atacicept, with no itching or severe injection-site reactions reported. No clinically significant changes in vital signs or laboratory parameters were reported.

In studies of 15 patients with relapsed or refractory B cell NHL [44] and 16 patients with advanced multiple myeloma or Waldenström’s macroglobulinaemia [45], participants were given atacicept (2, 4, 7 or 10 mg/kg) weekly for 5 weeks. Patients responding or with stable disease were eligible for further study treatment for up to 24 weeks or until disease progression. In both studies, atacicept was well tolerated, with no dose-limiting toxicities observed. Most adverse events were of mild or moderate severity with fatigue, injection-site bruising, dyspnoea, anorexia, diarrhoea and nausea being the most frequent. Fatigue was the only adverse event to be considered related to treatment in four NHL patients. No serious adverse events were considered to be linked to atacicept treatment. Few infections were reported; all were
mild or moderate in severity and none was considered related to atacicept treatment.
No anti-atacicept antibodies were detectable at the end of the study.

3. Conclusion

B cell-targeting therapies have been proven to be an effective approach to treating RA. BLyS and APRIL, which appear to be important in the pathogenesis of RA, bind to specific B cell receptors such as the TACI receptor and mediate B cell function, survival and antibody production. Atacicept, a recombinant receptor-Ig fusion protein, binds BLyS and APRIL and inhibits plasma cell and late-stage B cell development and survival but has no effect on B cell progenitors and memory cells. In clinical studies, atacicept is well tolerated in patients with RA with consistent and dose-related pharmacokinetic profiles. Dose-dependent decreases in immunoglobulins and relevant biomarkers, and reductions in mature B cells, were observed in atacicept-treated patients with RA. Initial clinical improvements in RA symptoms were also observed although data from larger clinical trials are needed to confirm the efficacy of atacicept. Results from these early clinical trials demonstrate the potential value of atacicept in the treatment of RA.

4. Expert opinion

There is now an increasing body of evidence to support a key role for B cells in the pathogenesis of RA. Furthermore, data from animal models and clinical studies also support an important role for the B cell growth factors BLyS and APRIL in the development of autoimmune disease. As BLyS and APRIL enhance the maturation, survival and proliferation of B cells, and the generation of plasma cells, neutralisation of BLyS and APRIL activity by atacicept can inhibit the later stages of B cell
differentiation and reduce the number of circulating mature B cells and plasma cells, and reduce Ig levels. Indeed, data from preclinical models showed that atacicept predominantly inhibits mature B cells and plasma cells, without affecting other lymphoid or myeloid populations. The safety profile of atacicept is good, and data from early-phase clinical trials are promising for using atacicept in the treatment of RA. Very recently, La and colleagues showed that serum levels of BLyS remained elevated in RA patients who did not respond to TNF-α blockade therapies, whereas serum BLyS levels declined in good responders [46]. Therefore, inhibition of BLyS activity by agents such as atacicept may be particularly beneficial for patients who do not respond to anti-TNF therapies.

Interest in the role of B cells in the pathogenesis of RA has led to the development of several other potential therapeutic agents that specifically target B cells by distinct mechanisms. Ocrelizumab [47] and ofatumumab [48] are fully humanised anti-CD20 mAbs. Since CD20 appears at the pre-B stage and disappears during differentiation to plasma cells, treatment with anti-CD20 therapies will not deplete stem cells and plasma cells, and serum Ig levels do not fall substantially during treatment. Indeed, the sparing of pathogenic antibody-producing plasma cells with anti-CD20 biological therapies may be one of the explanations for the disease relapse observed in RA patients treated with rituximab. In contrast, atacicept targets different subsets of B cells compared with rituximab, inhibiting B cells throughout their differentiation from naïve B cells to plasma cells. Therefore, atacicept may provide a clinically relevant decrease in pathogenic B cells while sparing some non-pathogenic B cells. In addition, atacicept may be safer than anti-CD20 monoclonal antibodies because of the less pronounced and prolonged B cell reductions. When used in combination with
anti-CD20 therapy, atacicept may facilitate broader and more prolonged B cell depletion. However, whether these differences will translate in terms of relative risk and benefit remains to be determined in controlled clinical trials.

Another biological therapy targeting B cell growth factors that has been tested in rheumatic diseases is belimumab, a humanised mAb against BLyS. As such, it inhibits B cell stimulation by BLyS, but not APRIL. In vivo models have demonstrated that antagonism of BLyS alone has no effect on bone marrow plasma cells whereas simultaneously blocking both APRIL and BLyS reduces bone marrow plasma cells [29]. Thus, the ability to inhibit the activity of APRIL in addition to BLyS by atacicept may prove advantageous, particularly in conditions such as RA and SLE, in which excess APRIL may play a role in pathogenesis [42, 49]. It remains to be seen, however, whether this difference will translate into biological or clinical benefits. In a phase II clinical study in patients with RA, belimumab demonstrated only a modest clinical benefit [50]. Reductions in B cells and rheumatoid factors were observed but ACR responses were relatively low with only a 13% increase with belimumab over placebo in the number of patients achieving an ACR20 response.

Other B cell-targeting therapies that are currently being evaluated for the treatment of RA include epratuzumab (a humanised mAb against B cell-restricted sialoglycoprotein, CD22) and single-chain polypeptides such as TRU-015.

Despite promising data from early clinical trials, the efficacy of atacicept in the treatment of RA needs to be confirmed in clinical trials of larger cohorts. Furthermore, the optimal timing, dose and dosing regimen for using atacicept in the
The treatment of RA remain to be determined [51]. Future clinical trials are also needed to identify predictors of response to enable the optimal use of the therapy.

Little is known about the medium- and long-term effects on the immune system of neutralising the activity of BLyS and APRIL. Atacicept has been shown to profoundly decrease Ig levels, and therefore concerns about long-term use exist, particularly regarding the risk of infections and possibly malignancies, which will need to be assessed by clinical studies in larger cohorts for longer durations.

Although anti-atacicept antibodies have so far not been detected in clinical trials, they were detected after long-term exposure in animals [30, 36] and had a neutralising effect on the administered drug. The co-administration of methotrexate may be useful in reducing the formation of neutralising antibodies and improving efficacy.

Finally, atacicept may also be efficacious in other autoimmune conditions such as SLE, multiple sclerosis, Sjögren’s syndrome, systemic sclerosis and glomerulonephritis, as well as B cell malignancies.

5. Acknowledgements

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systemic immune-based rheumatic disease.


An important preclinical study with a murine model of rheumatoid arthritis, which provided evidence for the role of BLyS and APRIL in modulating B cell development and demonstrated that atacicept was able to inhibit the progression of disease.


A study showing that simultaneous inhibition of BLyS and APRIL is required to decrease bone marrow plasma cells but has no effect on memory B cell survival and function.


A study which identified the BlyS-binding TACI receptor, its role in B cell autoimmune disease and the potential use of TACI-Ig as a treatment for autoimmune disease.


A phase I study showing that atacicept was well tolerated in healthy volunteers with non-linear pharmacokinetics and demonstrated biological activity.


A pivotal phase Ib study showing that atacicept treatment in patients with rheumatoid arthritis was well tolerated and biological activity was demonstrated with treatment-related decreases in immunoglobulin and rheumatoid factor levels and reductions in mature B cells.


A phase I study analysing the pharmacokinetic and pharmacodynamic profiles of atacicept in patients with rheumatoid arthritis.


A report showing that good clinical responses with anti-TNF therapies in patients with rheumatoid arthritis are associated with decreases in BlyS levels but similar decreases were not observed in poor responders to anti-TNF therapy indicating that inhibition of BlyS may be beneficial in patients who do not respond to anti-TNF therapies.


### Table 1. Expression of different B cell growth factor receptors and CD20 on human B cell subsets [24, 26–28].

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<th>Pro-B cell</th>
<th>Pre-B cell</th>
<th>Immature B cell</th>
<th>Transitional B cell</th>
<th>Mature B cell</th>
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BAFF-R, B cell-activating factor belonging to the TNF family receptor; BCMA, B cell-maturation antigen; TACI, transmembrane activator and calcium-modulating and cyclophilin-ligand interactor.
Table 2. Pharmacodynamic parameters in patients receiving placebo or atacicept 7 × 420 mg at 2-weekly intervals (data from Tak et al. [39])

<table>
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<td>IgG</td>
<td>79</td>
<td>94</td>
</tr>
<tr>
<td>IgM</td>
<td>46</td>
<td>74</td>
</tr>
<tr>
<td>Median RF levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA-RF</td>
<td>62</td>
<td>83</td>
</tr>
<tr>
<td>IgG-RF</td>
<td>59</td>
<td>71</td>
</tr>
<tr>
<td>IgM-RF</td>
<td>59</td>
<td>99</td>
</tr>
<tr>
<td>Median ACPA</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>B cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (CD19+)</td>
<td>94</td>
<td>75</td>
</tr>
<tr>
<td>Mature (IgD+/CD27−)</td>
<td>72</td>
<td>64</td>
</tr>
</tbody>
</table>

Day 85 represents the nadir in the immunoglobulin profiles; ACPA, anti-citrullinated protein antibodies; Ig, immunoglobulin; RF, rheumatoid factor.
Table 3. Pharmacokinetic parameters in patients receiving atacicept 7 × 420 mg at 2-weekly intervals (data from Nestorov et al. [40])

<table>
<thead>
<tr>
<th>Parameter (mean ± SD)</th>
<th>After first dose</th>
<th>After last dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free atacicept</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (hours)</td>
<td>107 ± 25.3</td>
<td>888 ± 301</td>
</tr>
<tr>
<td>$t_{max}$ (hours)</td>
<td>26.5 ± 7.6</td>
<td>2040 ± 5.7</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>5600 ± 3090</td>
<td>5280 ± 2480</td>
</tr>
<tr>
<td>AUC$_{0-336}$ (mg·h/L)</td>
<td>433 ± 177</td>
<td>924 ± 418</td>
</tr>
<tr>
<td><strong>Composite atacicept</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (hours)</td>
<td>97.6 ± 23.2</td>
<td>885 ± 140</td>
</tr>
<tr>
<td>$t_{max}$ (hours)</td>
<td>28 ± 9</td>
<td>2040 ± 7.6</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>7390 ± 3700</td>
<td>7320 ± 3530</td>
</tr>
<tr>
<td>AUC$_{0-336}$ (mg·h/L)</td>
<td>783 ± 295</td>
<td>1650 ± 504</td>
</tr>
</tbody>
</table>

AUC$_{336}$, area under the concentration–time curve from time 0 to 336 hours; $C_{max}$, maximum serum concentration; SD, standard deviation; $t_{1/2}$, terminal half-life; $t_{max}$, time to $C_{max}$. 
Figures legends

Figure 1. Mode of action of the B cell-targeting therapies atacicept (a) and rituximab (b) with a black cross indicating the affected B cell stages. Atacicept binds BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand) leading to reductions in mature, activated and antibody-producing B cell populations. Rituximab targets CD20 receptors on B cells, which are expressed on pre- through to memory B cells.

Figure 2. BLyS and APRIL are secreted by monocytes, neutrophils, dendritic cells and T cells. Expression of BLyS and APRIL is dependent on the cytokine environment and is stimulated by interferon (IFN)-γ, IFN-α and interleukin (IL)-10, and also by CD40 for dendritic cells. Soluble BLyS and APRIL usually form biologically active homotrimers, but can also form heterotrimers (HTs). BLyS, APRIL and HTs bind to specific B cell receptors (TACI, BCMA and BAFF-R) and trigger signals regulating B cell function (including proliferation and class switching to produce immunoglobulins) and survival. Binding of BLyS and APRIL to TACI, BCMA and BAFF-R induces the NF-κB signalling pathway, which plays a pivotal role in mediating inflammatory responses and facilitating adaptive immunity. Interaction with BCMA and TACI result in up- or downregulation of members of the Bcl-2 family of proteins that are involved in cell death, proliferation, survival, cell–cell interactions etc. APRIL also binds to proteoglycans (not shown), but the significance of this binding is not yet clear. Thus, BLyS and APRIL are key stimulators of B cell maturation, survival and proliferation, and are therefore targets for autoimmune disease therapy such as RA.
Title: Atacicept, a novel B cell-targeting biological therapy for the treatment of rheumatoid arthritis

Abbreviations:

ACR20  At least a 20% improvement in the American College of Rheumatology criteria

APRIL  A proliferation-inducing ligand

BAFF  B cell-activating factor belonging to the tumour necrosis family

BAFF-R  BAFF receptor

BCMA  B cell-maturation antigen

BLyS  B lymphocyte stimulator

CCP  Anti-cyclic citrullinated peptide

DAS  Disease activity score

DMARD  Disease-modifying antirheumatic drug

GC  Germinal centre

Ig  Immunoglobulin

mAb  Monoclonal antibody

MTX  Methotrexate

NHL  Non-Hodgkin’s lymphoma

PD  Pharmacodynamics

PK  Pharmacokinetics

RA  Rheumatoid arthritis

RF  Rheumatoid factor

SLE  Systemic lupus erythematosus

TACI  Transmembrane activator and calcium-modulating and cyclophilin-ligand interactor
TNF  Tumour necrosis factor

VAS  Visual analogue scale