Atacicept in relapsed/refractory multiple myeloma or active Waldenström’s macroglobulinemia: a phase I study

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BACKGROUND: Advanced multiple myeloma (MM) and Waldenström’s macroglobulinemia (WM) are incurable B-cell malignancies. This is the first full clinical report of atacicept, a fusion protein that binds to and neutralises the B-cell survival factors, B-lymphocyte stimulator (BlyS) and A proliferation-inducing ligand (APRIL), in MM and WM.

METHODS: In this open-label phase-I study, 16 patients with advanced disease (12 MM, 4 WM) received one cycle of five once-weekly subcutaneous injections of atacicept (2, 4, 7 or 10 mg kg−1). Patients with stable disease after cycle 1 entered an extension study (either two additional cycles (2, 4 and 7 mg kg−1 cohorts) or 15 consecutive weekly injections of atacicept 10 mg kg−1).

RESULTS: Atacicept was well tolerated, systemically and locally; the maximum tolerated dose was not identified. Of 11 patients with MM who completed initial treatment, five patients were progression-free after cycle 1 and four patients were progression-free after extended therapy. Of four patients with WM, three patients were progression-free after cycle 1. Consistent with atacicept’s mechanism of action, polyclonal immunoglobulin isotypes and total B cells were reduced. Bone-marrow density, myeloma cell numbers and plasma concentrations of soluble CD138 also decreased.

CONCLUSION: Atacicept is well tolerated in patients with MM and WM, and shows clinical and biological activity consistent with its mechanism of action.

Keywords: atacicept; multiple myeloma; Waldenström’s macroglobulinemia; BlyS; APRIL

Multiple myeloma (MM) is the second most prevalent blood cancer, accounting for 10% of haematological malignancies. The median age at diagnosis is 68 years and the incidence increases with advancing age (Ferlay et al., 2004). Among patients treated with conventional chemotherapy, the median survival is about 42 months (Blade et al., 1994). In patients younger than 65 years, high-dose chemotherapy supported by autologous stem cell transplantation increases the median survival to 60 months (Harousseau and Moreau, 2007). Despite recent innovations in approaches to therapy, options remain limited for the majority of patients.

Waldenström’s macroglobulinemia (WM) is a B-cell malignancy, which results from a clonal proliferation of lymphocytes and plasma cells that produce monoclonal immunoglobulin (Ig) M, and our understanding of this clinicopathological entity has improved in recent years (Vitolo et al., 2008; Dimopoulos et al., 2009). The median age at presentation is 63 years (Dimopoulos et al., 2000). The Fourth International Workshop on WM reviewed treatment guidelines for patients with WM who require systemic therapy; current primary treatments include alkylating agents, nucleoside analogues and immunotherapies, as single agents and in combination regimens (Dimopoulos et al., 2009). The need for and development of new therapies for patients with WM was further discussed at the recent Fifth International Workshop on WM (Treon et al., 2009).

B-lymphocyte stimulator (BlyS, CD257, also known as B-cell activating factor (BAFF)) (Schneider et al., 1999) and A proliferation-inducing ligand (APRIL, CD256) stimulate the growth of primary myeloma cells (Moreaux et al., 2004; Novak et al., 2004). BlyS and APRIL share two receptors, trans-membrane activator and CAML interactor (TACI, CD267) (Von Bulow and Bram, 1997) and B-cell maturation antigen (BCMA, CD269) (Gras et al., 1995). BlyS also binds to a third receptor, BAFF-R (also known as BR3, CD268) (Thompson et al., 2001). Most myeloma cell lines and primary myeloma cells express one or more of these receptors for BlyS (Novak et al., 2004; Moreaux et al., 2007, 2009) and also aberrantly express BlyS and APRIL mRNA (Moreaux et al., 2004). BlyS and APRIL are also produced in large amounts in the tumour bone marrow environment, primarily by myeloid cells, monocytes and osteoclasts (Moreaux et al., 2005; Abe et al., 2006; Tai et al., 2006; Yaccoby et al., 2008). Exogenous BlyS and APRIL act as
Atacicept in MM and WM
J-F Rossi et al

MATERIALS AND METHODS

Study design and interventions

We report the results of two studies conducted in one centre in France. The protocols were developed in collaboration with, and approved by, an independent ethics committee, and the studies were carried out in accordance with the Declaration of Helsinki, the standards of the International Conference on Harmonization, Guideline for Good Clinical Practice and local regulations. Patients gave written informed consent for participation in each study. This study was initiated in November 2004 and at that time was not registered in a clinical trial registry.

Adults (≥18 years of age) with confirmed relapsed and/or refractory MM or progressive WM were recruited into an exploratory single-arm, open-label, dose escalating, repeat-dose study (defined as cycle 1). Eligible patients were enrolled in sequential cohorts to receive one cycle of five weekly subcutaneous injections of atacicept (Merck Serono S.A. – Geneva, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany) and ZymoGenetics Inc., Seattle, WA, USA) at doses of 2 mg kg⁻¹ (cohort 1, 3 patients), 4 mg kg⁻¹ (cohort 2, 3 patients), 7 mg kg⁻¹ (cohort 3, 3 patients) or 10 mg kg⁻¹ (cohort 4, 7 patients). Escalation to the next dose cohort and identification of the maximum tolerated dose (MTD) for atacicept depended on the frequency of dose-limiting toxicities (DLTs) in the preceding cohort and approval by the safety committee.

Patients who completed cycle 1, demonstrated at least stable disease after a 4-week follow-up period and had not experienced any DLTs were eligible to enter the extension study. During the extension study, patients received either two additional cycles of atacicept subcutaneously (five weekly injections), at the same dose as cycle 1, separated each by a 4-week wash-out period (cohorts 1-3) or one continuous cycle of 15 weekly injections of atacicept 10 mg kg⁻¹ (cohort 4). After the extension treatment cycles, patients entered a 4-week post-treatment period and a subsequent 2-month follow-up period. Figure 1 summarises the study design and patient disposition.

Patients

The main study inclusion criteria were: measurable disease, at least one previous regimen of treatment (chemotherapy and/or stem cell transplantation), Eastern Cooperative Oncology Group performance status of 0-2, life expectancy of at least 6 months, adequate hepatic and renal functions (serum aspartate aminotransferase or alanine aminotransferase activity ≤2.5 times the upper limit of normal (ULN) or serum total bilirubin ≤1.5 times ULN, creatinine ≤2 times ULN) and stable haematological parameters (platelet count of ≥50,000 mm⁻³, haemoglobin concentration of ≥8 g 100 ml⁻¹ and absolute neutrophil count of ≥1000 mm⁻³) and the willingness to use acceptable methods of contraception during the study and until 3 months after the last dose of atacicept. The main exclusion criteria included: non-secretory myeloma, amyloidosis, active infection, stem cell transplantation during the study and until 3 months after the last dose of atacicept during the study and until 3 months after the last dose of atacicept, previous history of congestive heart failure, significant cardiac ejection fraction abnormalities and presence or history of other types of cancer.

Safety

Throughout both studies, safety was assessed by adverse event (AE) reports, occurrence of DLTs, direct physical examination and clinical laboratory tests. Owing to the mechanism of action of atacicept, AEs in the system organ class (SOC) of ‘Infections and infestations’ were closely monitored.

DLTs were defined by using the Common Toxicity Criteria for Adverse Events (Version 3, 12 December 2003). Non-haematological DLTs: (1) any serious AE unless unrelated to the study drug and (2) any grade 3 AE possibly, probably or definitely related to the study drug. Haematological DLTs: (1) any AE of grade 3 possibly, probably or definitely related to the study drug (except B-cell lymphopenia using the grading scale for haematological toxicity from the National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukaemia (Cheson et al, 1996), which was an expected effect of BlyS and APRIL depletion; (2) hypersensitivity reactions of grade 2 (considered dose limiting for an individual); or (3) grade 3 or 4 hypersensitivity.
reactions reported in multiple patients at the same dose level (considered DLTs for the study). Injection-site reactions were considered as non-haematological events and were evaluated using non-haematological DLT criteria. The assessment of anti-atacicept binding antibodies was carried out before entry into the study and 2–3 months after the last treatment dose.

Pharmacokinetic assessment

Serum concentrations of free atacicept, atacicept–BLyS complex and total atacicept (free plus atacicept–BLyS complex) were assessed in all patients before injection and weekly after injection during cycle 1, according to previously published methods (Tak et al, 2008). Atacicept–APRIL complexes were not assessed in this study.

Response evaluation

Response evaluation was carried out 4 weeks after treatment cessation following both cycle 1 and the extension study, using published response criteria (Bladé et al, 1998; Cheson et al, 1999). Magnetic resonance imaging, computerised (axial) tomography scan and/or ultrasound scan (for patients with WM only) were carried out in addition to skeletal X-ray surveys (optional).

Biological assessments

Pharmacodynamic parameters included concentrations of M-protein (by electrophoresis and immunofixation), β2-microglobulin, polyclonal Igs and C-reactive protein (CRP) in serum and free light chain in serum and urine. Bone marrow aspirates were carried out at screening, at the end of treatment and at the end of the 4-week follow up during cycle 1, and at the end of treatment during the extension study (Figure 1). Phenotyping of lymphocyte lineages and myeloma cells was carried out by Esoterix (Mechelen, Belgium) on peripheral blood and bone marrow samples using flow cytometry analysis and the cell-specific antibodies CD3, CD4, CD8, CD14, CD19, CD27, CD38, CD45, CD56, kappa and lambda. Soluble Syndecan-1 (sCD138) was measured in patient sera using an enzyme-linked immunosorbent assay (ELISA) with 8 ng ml⁻¹ sensitivity (Diaclone, Besançon, France). Serum concentrations of free BLyS and APRIL were assessed using ELISA methodology (Tak et al, 2008) before treatment, but not during treatment, as the presence of atacicept interfered with the assays.

Data analysis and statistics

The safety population comprised all patients who received at least one injection of atacicept. All efficacy analyses were carried out in the efficacy population, which included all patients who received ≥4 injections of atacicept during cycle 1. In the extension study, patients who received at least one injection of atacicept were included in the efficacy analyses. Owing to the exploratory nature of this trial, descriptive statistics and graphical representations were used to summarise data.

The statistical significance of the decrease in polyclonal Ig levels after atacicept treatment, of the percentage of myeloma cells in the bone marrow at the end of cycle 1, and of the plasma levels of sCD138 at the end of each cycle, were analysed using Wilcoxon’s test for pairs.

RESULTS

Safety

Sixteen patients (out of 18 patients screened for participation) entered cycle 1 (Figure 1) and were included in the safety population. Demographic and baseline disease characteristics are shown in Table 1. Treatment with atacicept at the four dose levels was well tolerated both systemically and locally in all patients with MM or WM, during cycle 1 and in all extension schedules, with most AEs being of mild or moderate severity. The MTD of atacicept was not identified, as no DLTs were observed. All patients experienced at least one AE during the treatment period of cycle 1. The severity of the 57 treatment-emergent AEs reported was as follows: 45 mild, 10 moderate and 2 severe. The 10 (17.5%) AEs of moderate severity that occurred during the treatment period of cycle 1 are listed in Table 2. The 2 (3.5%) severe AEs that occurred during the treatment period of cycle 1 were one event of lung disorder (2 mg kg⁻¹) and one of motor dysfunctions (10 mg kg⁻¹), both of which were assessed as unrelated to study treatment. The case of severe neuropathy was reported to have a possible infectious component and the patient was hospitalised and treated with antibiotics. A thoracic scan showed a large tumoral mass with underlying osteolysis. This patient was hospitalised with neuropathy on two further occasions and treated with antibiotics; sequelae of progressive

| Characteristic | Statistics | Overall |
|---------------|------------|---------|
| Age, years    | Mean (s.d.) 67.9 (6.7) |
| Sex, n (%)    | Male 9 (56.2) |
| Disease type at diagnosis, n (%) | MM 12 (75.0) |
| Disease stage at diagnosis for patients with MM, n (%) | Stage I 2 (16.7) |
| Disease status at entry, n (%) | Refractory 5 (31.3) |
| β2-microglobulin at baseline (mg l⁻¹) | Mean (s.d.) 2.7 (1.1) |
| Type of Ig for patients with MM, n (%) | lgA 6 (50.0) |
| Serum M-protein concentration (g l⁻¹) | Lambda 5 (41.7) |
| Bone marrow plasma cell cytogenic abnormalities, n (%) | Yes 6 (37.5) |
| Number of previous lines of anti-tumour treatments, n (%) | 0 0 (0.0) |
| Transplant history for patients with MM, n (%) | None 3 (25.0) |

Abbreviations: Ig = immunoglobulin; MM = multiple myeloma; s.d. = standard deviation; WM = Waldenström’s macroglobulinemia. n = 16.

| Dose cohort | Treatment-emergent adverse events of moderate severity |
|-------------|------------------------------------------------------|
| 2 mg kg⁻¹   | None                                                  |
| 4 mg kg⁻¹   | 1 haematoma                                           |
| 7 mg kg⁻¹   | 1 bone pain; 1 epiploic appendagitis; and 1 multiple myeloma |
| 10 mg kg⁻¹  | 2 arthropalgia (in 1 patient); 1 back pain; 1 asthma; 1 pain; and 1 fungal infection |

Table 1 Demographic and baseline disease characteristics (safety population)

Table 2 Treatment-emergent adverse events of moderate severity occurring during the treatment period of cycle 1, by dose regimen (safety population)
disease and pleural effusion were noted. The patient with motor dysfunction was withdrawn from treatment after receiving two doses of atacicept. The patient had medullar compression due to myeloma metastasis. Surgery was performed to relieve the compression and the patient was transferred to the haematology unit and discharged after 1 month.

Four patients each experienced one serious AE (pneumopathy, epiploic appendagitis, progression of MM and motor dysfunction) during the cycle 1 treatment period, none of which was considered to be related to atacicept. The patient with progression of MM died during the follow-up period of cycle 1; the cause of death was recorded as MM. No serious AEs were reported during the extension study.

Few events were reported in the SOC 'Infections and infestations' during cycle 1 or the extension study; all of these were mild or moderate in severity and none of these events was considered to be related to atacicept treatment. The events in this SOC included upper respiratory and urinary tract infection, gastroenteritis, influenza, rinitis, nasopharyngitis, fungal infection (one patient reported mild inguinal mycosis, which resolved without intervention) and bronchitis.

None of the 13 patients tested was positive for anti-atacicept binding antibodies at study end.

Pharmacokinetics

In general, free atacicept, total atacicept and atacicept–BLyS complex behaved consistently across the dose cohorts studied (Figure 2A–C). A mild non-linearity in the pharmacokinetic variables was observed (data not shown), probably because of the mediation of the kinetics of atacicept by its ligands, as reported previously (Munafo et al., 2007; Tak et al., 2008). There was a slightly higher accumulation of atacicept–BLyS complex and total atacicept compared with that of free atacicept, yielding a moderate accumulation ratio of approximately two for the five consecutive doses in cycle 1.

Response evaluation

Among the 12 patients with MM who entered the initial treatment phase, 11 completed cycle 1 (patients 1, 2, 3, 5, 7, 8, 11, 13, 14, 17 and 18) and were analysed for response 4 weeks after treatment cessation (efficacy population). Five patients (45%, patients 2, 3, 11, 13 and 18) were progression free and received additional treatment during the extension study (Figure 1 and Table 3). At the end of the extension study, four patients (36%, patients 2, 3, 11 and 18) were progression free. For these four patients with stable disease, all the parameters considered for treatment response, which included β2-microglobulin, calcium, albumin, haemoglobin and creatinine levels, and white blood cell count, as well as the M-protein concentrations, remained stable. No new bone lesions were reported in these patients.

All four patients with WM completed cycle 1 (patients 4, 6, 10 and 12) and were analysed for response (efficacy population). Three patients were progression free at the end of cycle 1 (patients 4, 10 and 12; Figure 1 and Table 3). At the end of the extension study, two patients (patients 10 and 12) were progression free (one patient had a minimal response and the other patient had stable disease). No progression of the tumour mass was observed in the two patients who had lymph node involvement at study entry.

Biological responses

Polyclonal IgM and IgA were evaluated in patients with IgG MM, polyclonal IgM and IgG in patients with IgA MM and polyclonal IgG and IgA in patients with WM. Consistent with the mechanism of action of atacicept, a significant decrease of the polyclonal Ig isotypes (median decrease 40%, range 10–70%) was seen in

**Figure 2** (A) The change in median free atacicept concentration during disease evolution in patients with multiple myeloma (MM) or Waldenström's macroglobulinaemia (WM). (B) The change in median total atacicept (free plus atacicept–BLyS complex) concentration during disease evolution in patients with MM or WM. (C) The change in median atacicept–BLyS complex concentration during disease evolution in patients with MM or WM. 1 U/ml corresponds to 1.82 ng ml⁻¹ of atacicept to 0.44 ng ml⁻¹ of B-lymphocyte stimulator (BLyS) in a 1:3 molar ratio. (D) Mean percent change from baseline in total B cells (CD19+ /CD20+) in patients with MM or WM.
6 out of 11 patients with MM (patients 2, 3, 5, 8, 14 and 18) and 3 out of 4 patients with WM (patients 4, 10 and 12) \((P<0.05)\) at the end of cycle 1. The magnitude of the reduction appeared to be homogeneous across the three isotypes studied, and was notable across all dose and disease groups. In addition, this reduction lasted until the end of follow up. Representative results for polyclonal IgG are shown in Figure 3A for the six patients with IgG-secreting MM, and in Figure 4A for the four patients with WM. Consistent with the decrease in polyclonal Ig, a dose-dependent reduction in total circulating B cells \((CD45 \text{dim CD38}^+ \text{ M-protein})\) was observed (Figure 2D). Neither natural killer cell nor T-lymphocyte subset counts were altered (results not shown).

Five patients with MM had stable or slightly decreased concentrations of M-protein during cycle 1 (patients 2, 3, 11, 13 and 18; Figure 3B). Stabilisation of M-protein concentrations was confirmed in four patients who received extended treatment (patients 2, 3, 11 and 18; Figure 3B). The corresponding kappa and lambda light-chain serum concentrations followed a similar trend (data not shown). Consistent with the stabilisation/reduction in M-protein in five patients, there was a decrease in the percentage of CD45dim CD38 \(^+\) \(\text{MM cells in the bone marrow at the end of cycle 1} (P<0.05, \text{Figure 3C})\). Furthermore, sCD138 concentration was reduced, most strikingly in patients receiving the highest dose of atacicept who entered the extension study. A decrease in sCD138 concentration was consistently seen at the end of the first treatment cycle in this cohort of patients \((P<0.05, \text{Figure 3D})\). Two patients with stable disease during the extension study had very low concentrations of sCD138 or levels below the limit of sensitivity of the assay, up to 2 months after treatment termination. This decrease of sCD138 measurement was not due to the interference of atacicept with sCD138 dosage, as atacicept can bind sCD138. Indeed, adding graded concentrations of atacicept in the ELISA did not change sCD138 titration (results not shown). The biological effect of atacicept was more pronounced in patients with WM. Of those who entered the extension study, one patient had a minimal response \((\text{decrease of } \geq 25\% \text{ from baseline in M-protein concentration})\) and a noticeable decrease was seen in the serum M-protein concentrations in the remaining two patients during the first month of treatment and throughout the extension study (Figure 4B). However, the optimal biological dose \((\text{defined as a dose leading to } > 25\% \text{ decrease in M-protein concentration at day 57 of the first treatment cycle})\) was not identified for patients with MM or WM.

Atacicept did not affect the inflammatory biomarkers, CRP \((\text{range at baseline: } 2 – 400 \text{ mg l}^{-1})\) or erythrocyte sedimentation rate \((\text{data not shown})\).

Of the 16 patients tested at baseline, 13 had measurable levels of free APRIL \((\geq 25 \text{ ng ml}^{-1})\). In contrast, only three patients had baseline free BLyS concentrations above the limit of quantification \((1.6 \text{ ng ml}^{-1})\). In this small number of patients, no correlations were apparent between baseline levels of free APRIL and biological or clinical response criteria.

**DISCUSSION**

This is the first full report of atacicept treatment in patients with MM and WM. A preliminary report has previously been presented \((\text{Rossi et al, 2005})\). Atacicept at doses of up to 10 mg kg\(^{-1}\) was generally well tolerated and had a favourable safety profile. However, because of the small population size and relatively low numbers of AEs, no definitive patterns in the frequency or nature of events could be determined with respect to dose.

One of the primary objectives of cycle 1, the identification of the MTD of atacicept, was not achieved: the maximum dose that could be delivered by subcutaneous injection was 10 mg kg\(^{-1}\), and this dose did not elicit DLTs. Similarly, no DLTs were observed using repeated doses of atacicept up to 10 mg kg\(^{-1}\) in a study in patients with advanced B-cell lymphomas in which, although atacicept showed biological activity, clinical responses were not observed \((\text{Ansell et al, 2008})\). In this study, it is encouraging that, as well as being generally well tolerated up to 10 mg kg\(^{-1}\), both biological and clinical responses were observed.

Of particular note, a decrease across all measured polyclonal Ig isotypes was seen in most patients, concomitant with a notable, but incomplete, decline in circulating Ig-producing cells. Atacicept has been associated with dose-dependent reductions in levels of polyclonal Ig isotypes and circulating B cells in patients with rheumatoid arthritis \((\text{Tak et al, 2008})\), and systemic lupus erythematosus \((\text{Dall’Era et al, 2007})\). B cells mature into plasmablasts in germinal centers of lymphoid organs, these cells

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**Table 3** Clinical responses in patients with multiple myeloma (MM) and Waldenström’s macroglobulinemia (WM) who completed the initial treatment period in cycle 1

| Patient number | Dose mg kg\(^{-1}\) | MM isotype | Cycle 1 | Extension study* |
|----------------|---------------------|------------|---------|-----------------|
| **Patients with MM** | | | | |
| 1 | 2 | IgG kappa IIA | Progressive disease | Stable disease |
| 2 | 2 | IgG lambda IIA | Stable disease | Stable disease |
| 3 | 2 | IgA lambda IIA | Progressive disease | Stable disease |
| 4 | 4 | IgD lambda IA | Progressive disease | Stable disease |
| 5 | 7 | IgG lambda IA | Progressive disease | Stable disease |
| 6 | 7 | IgA lambda IIA | Stable disease | Progressive disease |
| 7 | 10 | IgG kappa IIA | Stable disease | Stable disease |
| 8 | 10 | IgA kappa IIA | Progressive disease | Stable disease |
| 9 | 10 | IgA kappa IIA | Progressive disease | Stable disease |
| 10 | 10 | IgA kappa IIA | Progressive disease | Stable disease |
| 11 | 10 | IgA kappa IIA | Progressive disease | Stable disease |
| 12 | 10 | IgA kappa IIA | Progressive disease | Stable disease |
| **Patients with WM** | | | | |
| 4 | 4 | NA | Stable disease | Progressive disease |
| 6 | 4 | NA | Stable disease | Progressive disease |
| 10 | 7 | NA | Stable disease | Stable disease |
| 12 | 10 | NA | Stable disease | Minimal response |

Abbreviations: Ig = immunoglobulin; NA = not applicable. *Patients who completed cycle 1, demonstrated at least stable disease after a 4-week follow-up period and had not experienced any dose-limiting toxicity were eligible to enter the extension study.
Clinical Studies

Differentiation (O

activation by BLyS/APRIL is mandatory for plasma cell differentiation, supported by data from experiments in mice showing that BCMA is required for the long-term survival of plasma cells. This suggestion is buttressed by the observation that atacicept suggests that BLyS and APRIL may be critical factors for the survival of plasma cells.

Long-term treatment with anti-CD20 antibody can profoundly deplete B cells and the generation of new plasma cells, without affecting the circulating polyclonal Ig and the pool of plasma cells. The decrease in polyclonal Ig with atacicept treatment suggests that it affects the numbers of both mature B cells and plasma cells. This is of particular interest, given the proposed role of sCD138 in the accumulation of APRIL in the bone marrow stroma, the binding of APRIL to its receptors and the ensuing mediation of plasma-cell survival.

These convergent observations suggest that atacicept inhibits MM cell survival within the bone marrow microenvironment rather than merely altering monoclonal Ig synthesis by MM cells, as predicted from in vitro treatment studies using primary myeloma cells. In addition, atacicept did not affect the inflammation markers often elevated in B-cell malignancies, suggesting that it does not interfere with the interleukin-6-dependent pathway. The lack of a correlation between free APRIL levels at baseline and MM cell survival suggests that it does not affect the overall APRIL levels.

Figure 3  

(A) The percentage change from baseline in polyclonal immunoglobulin-G (IgG) component throughout cycle 1 and the extension study for patients with multiple myeloma (MM): Patients 1, 2, 7, 11 and 13 from the efficacy population are not shown as they had IgG monoclonal component. (B) The change in M-protein concentration (disease specific marker) throughout cycle 1 and the extension study in patients with MM who demonstrated stable disease after cycle 1. (C) The change in the proportion of MM cells (CD45dim CD38 brightly) in the bone marrow throughout cycle 1 and the extension study, as determined by flow cytometry analysis, in patients with MM who demonstrated stable disease after cycle 1. (D) The change in soluble Syndecan-1 (sCD138) concentration throughout cycle 1 and the extension study in patients with MM who received atacicept 10 mg kg⁻¹ (cohort 4).

Consistent with these serum marker features were noticeable decreases in the percentage of bone marrow CD45dim CD38 brightly MM cells and circulating levels of sCD138, reflecting the production of sCD138 by these cells in the bone marrow. This is of particular interest, given the proposed role of sCD138 in the accumulation of APRIL in the bone marrow stroma, the binding of APRIL to its receptors and the ensuing mediation of plasma-cell survival.

These convergent observations suggest that atacicept inhibits MM cell survival within the bone marrow microenvironment rather than merely altering monoclonal Ig synthesis by MM cells, as predicted from in vitro treatment studies using primary myeloma cells. In addition, atacicept did not affect the inflammation markers often elevated in B-cell malignancies, suggesting that it does not interfere with the interleukin-6-dependent pathway. The lack of a correlation between free APRIL levels at baseline and MM cell survival suggests that it does not affect the overall APRIL levels.

Then migrate to the bone marrow or mucosa where they differentiate into plasma cells, which can survive for up to 20 years, thus ensuring the continuity of humoral immunity (Hofer et al., 2006). The maintenance of the plasma cell pool has been shown to be independent of memory B cells (Ahuja et al., 2008). Long-term treatment with anti-CD20 antibody can profoundly deplete B cells and the generation of new plasma cells, without affecting the circulating polyclonal Ig and the pool of plasma cells (Ahuja et al., 2008). Thus, the decrease in polyclonal Ig with atacicept suggests that BLyS and APRIL may be critical factors for the long-term survival of plasma cells. This suggestion is supported by data from experiments in mice showing that BCMA activation by BLyS/APRIL is mandatory for plasma cell differentiation (O’Connor et al., 2004), and that atacicept treatment can reduce the numbers of both mature B cells and plasma cells (Ramanujam et al., 2006; Benson et al., 2008). Stabilisation or a slight reduction in M-protein concentration was seen during the first treatment cycle in almost half of the patients with MM, and was maintained in the majority of patients who entered the extension study. This pattern was repeated for corresponding serum concentration profiles of kappa or lambda light chains.
The biological effect of atacicept treatment appeared more marked and consistent among patients with WM, with three out of four patients showing a noticeable decrease in M-protein concentration during the first month of treatment. However, a rise in M-protein levels was seen in the fourth patient. A paradoxical concentration during the first month of treatment. However, a rise in M-protein levels was seen in the fourth patient. A paradoxical rise in serum IgM levels should be taken into consideration in future trials investigating the effects of atacicept in patients with WM.

The relatively low circulating concentrations of BlyS observed at baseline are in contrast with previous reports (Moreaux et al., 2004). However, peripheral BlyS concentrations may not reflect the local BlyS production in the bone marrow microenvironment. Increased BlyS production could explain the increased concentration of serum atacicept–BlyS complexes. Indeed, these complexes reflect the BlyS binding load, which may explain why a resumption of disease progression, rather than a rebound phenomenon, was observed after treatment cessation.

Five of the patients with MM who completed the first treatment cycle had stable disease, and four of these maintained stable disease after the extension treatment period. In addition, three of the four patients with WM had stable disease after completion of the first treatment cycle, and two of these had either a minimal response or stable disease after the extension treatment period. These findings, together with the favourable safety profile and evidence of the biological activity of atacicept in this phase-I trial, may justify further investigation. Although significant infection-related AEs have not been associated with atacicept treatment here or in initial studies in other indications (Dall’Era et al., 2007; Ansell et al., 2008; Tak et al., 2008), surveillance for effects on infection should remain a high priority because of the possible association between suppression of polyclonal B cells and infection. Basic scientific investigations should be focused on characterising the role of atacicept in the MM bone-marrow microenvironment, specifically in the sCD138 matrix.

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DISCLOSURE

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