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Peer reviewed

Original Article

Integrated safety profile of atacicept: an analysis of pooled data from the atacicept clinical trial programme

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Abstract

Objective. To characterize the overall safety profile of atacicept, we conducted an integrated analysis of pooled safety data from all 17 clinical studies to date.

Methods. Three data sets were used to investigate safety endpoints: a double-blind placebo-controlled set ($n = 1568$), an SLE set ($n = 761$) and a full analysis set ($n = 1845$; including all 17 studies).

Results. Of 1568 patients in the double-blind placebo-controlled-set, 30.8% received placebo, and 8.2, 24.5 and 36.5% received atacicept 25, 75 and 150 mg, respectively. Treatment-emergent adverse event (TEAE) rates (adjusted by treatment-exposure) were generally higher with atacicept vs placebo, but no consistent association was found between atacicept dose and specific TEAEs or mortality. Serious infection and serious TEAE rates were similar for atacicept and placebo. The TEAE-related discontinuation rates were higher with atacicept vs placebo (16.1 vs 10.9/100 patient-years). In the full analysis set, 11 deaths occurred during treatment. Across indications, exposure-adjusted mortality rates/100 patient-years (95% CI) were 3.60 (0.90, 14.38), 0.34 (0.05, 2.43) and 1.18 (0.49, 2.82) with atacicept 25, 75 and 150 mg, respectively, and 0.44 (0.06, 3.12) with placebo. In SLE patients, exposure-adjusted mortality rates were 1.45 (0.54, 3.87) with atacicept 150 mg and 0.78 (0.29, 2.07) across all atacicept-treated patients. No deaths occurred with atacicept 75 mg or placebo. In the SLE and double-blind placebo-controlled sets, pharmacodynamic effects of atacicept were not associated with increased infection rates.

Conclusion. The results of this integrated safety analysis support further development and evaluation of atacicept in selected patients for whom potential benefits might outweigh risks.

Key words: atacicept, autoimmune diseases, safety, B-cell targeting, clinical trials, systemic lupus erythematosus, adverse events

Key message

- Integrated analysis of atacicept clinical studies supports further evaluation in selected patients if benefits outweigh risks.

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Introduction

Atacicept is a fully human, soluble fusion protein consisting of a transmembrane activator and calcium modulating cyclophilin ligand (CAML) interactor extracellular ligand-binding domain and a modified Fc-IgG1 domain [1], which has been shown to bind and neutralize the cytokines B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) *in vitro* [2]. BLyS

and APRIL are key modulators of B-cell activity [3–6], and their levels have been shown to be elevated alongside dysregulated B-cell activity in various autoimmune conditions, including SLE [7, 8].

In *in vitro* studies and preclinical animal models, dual inhibition of BLyS and APRIL by atacept was more potent than blocking of BLyS alone, resulting in decreased levels of autoreactive B cells, plasma cells and Ig [9–11]. Vigolo *et al.* [12] recently demonstrated that atacept binding is not negatively affected by the loop region of the BLyS 60-mer (a naturally occurring cleaved human BLyS), which was shown temporarily to prevent binding of the anti-BLyS antibody, belimumab. Consistent with these data, atacept reduces serum Ig levels in a dose-dependent manner in humans [13–15].

Atacept has been investigated clinically in healthy volunteers [16, 17], patients with B-cell malignancies, such as chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, multiple myeloma and Waldenström's macroglobulinaemia [18–20], and patients with autoimmune conditions, including RA [21–24], multiple sclerosis (MS) [25], LN [26], optic neuritis (ON) [27] and, most recently, SLE [14, 15, 28]; a study in IgA nephropathy is currently ongoing (NCT02808429).

Although the primary endpoints in two large SLE studies [APRIL-SLE (Phase II/III; NCT00624338) and ADDRESS II (Phase IIb; NCT01972568)] were not met, *post hoc* analyses suggested that weekly treatment with s.c. atacept 150 mg had beneficial effects on disease activity and response rates, particularly in ADDRESS II, in patients with high disease activity (HDA; SLEDAI-2K \geq 10) at screening [14, 15]. In APRIL-SLE, atacept 150 mg reduced disease flare rates and prolonged the time to a new flare vs placebo [14]. However, two infection-related deaths in this group prompted early cessation of enrolment within the 150 mg dose arm. In ADDRESS II, a greater proportion of HDA patients treated with atacept had SLE responder index [SRI]-4 and SRI-6 responses and a reduced risk for severe flare (as assessed by BILAG index A manifestation and by the Safety of oestrogens in Lupus Erythematosus National Assessment [SELENA]-SLEDAI flare index) compared with placebo-treated patients [15]. In both studies, the frequency of serious treatment-emergent adverse events (TEAEs; including infections) was comparable between atacept and placebo groups [14, 15].

Safety findings, including unexpected decreases in IgG levels (APRIL-LN), serious infections (APRIL-LN and APRIL-SLE) including two cases of pneumonia with fatal outcome (APRIL-SLE), myocardial infarction with fatal outcome (Study 014 in LN) and increase of disease activity (ATAMS in MS and ATON in ON) [14, 25–27] were observed in earlier studies of atacept in autoimmune diseases; these studies were partly (APRIL-SLE; atacept 150 mg arm) or fully terminated as a consequence. After these observations, risk mitigation measures were implemented for the ADDRESS II study in SLE, its long-term extension and other subsequent studies. These measures included medical monitor reviews of patient screening data to confirm eligibility and up-to-date

vaccinations against pneumococcus and seasonal influenza. It is worth noting that infection rates were lower in the ADDRESS II study and its extension than those observed in APRIL-SLE, and no study-drug-related deaths were reported [15, 28].

Given the observed benefit of atacept, particularly in SLE patients with HDA, and the observed safety profile of atacept in the ADDRESS II study and its long-term extension, there is rationale for further characterization of the overall safety profile of atacept. This will serve as a foundation for future studies to explore the efficacy of atacept further in specific subsets of patients, in whom the benefits might outweigh the potential risks. Therefore, we conducted an integrated analysis of safety data from all atacept clinical studies to date to characterize the overall safety profile of atacept. Specifically, we sought to investigate adverse event (AE) and infection rates with atacept vs placebo in double-blind placebo-controlled (DBPC) trials, and mortality rates across all atacept studies.

Methods

Studies included in the analysis

Data from 17 clinical studies of atacept were included in this integrated analysis (Fig. 1). Twelve studies were conducted in patients with autoimmune diseases (SLE [14, 15, 28–30], LN [26], RA [21–24], MS [25] and ON [27]), three studies focused on patients with B-cell malignancies (chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, multiple myeloma and Waldenström's macroglobulinaemia) [18–20], and two were conducted in healthy volunteers [16, 17]. All studies have been described previously and are summarized in [Supplementary Table S1](#), available at *Rheumatology Advances in Practice* online. Briefly, in the DBPC Phase II and Phase II/III studies, atacept was administered s.c. weekly at doses of 25, 75 or 150 mg, and patients received concomitant standard-of-care therapies as appropriate. Study protocols were in accordance with the Declaration of Helsinki and were approved by the appropriate institutional review boards or ethics committees; written informed consent was provided by all patients.

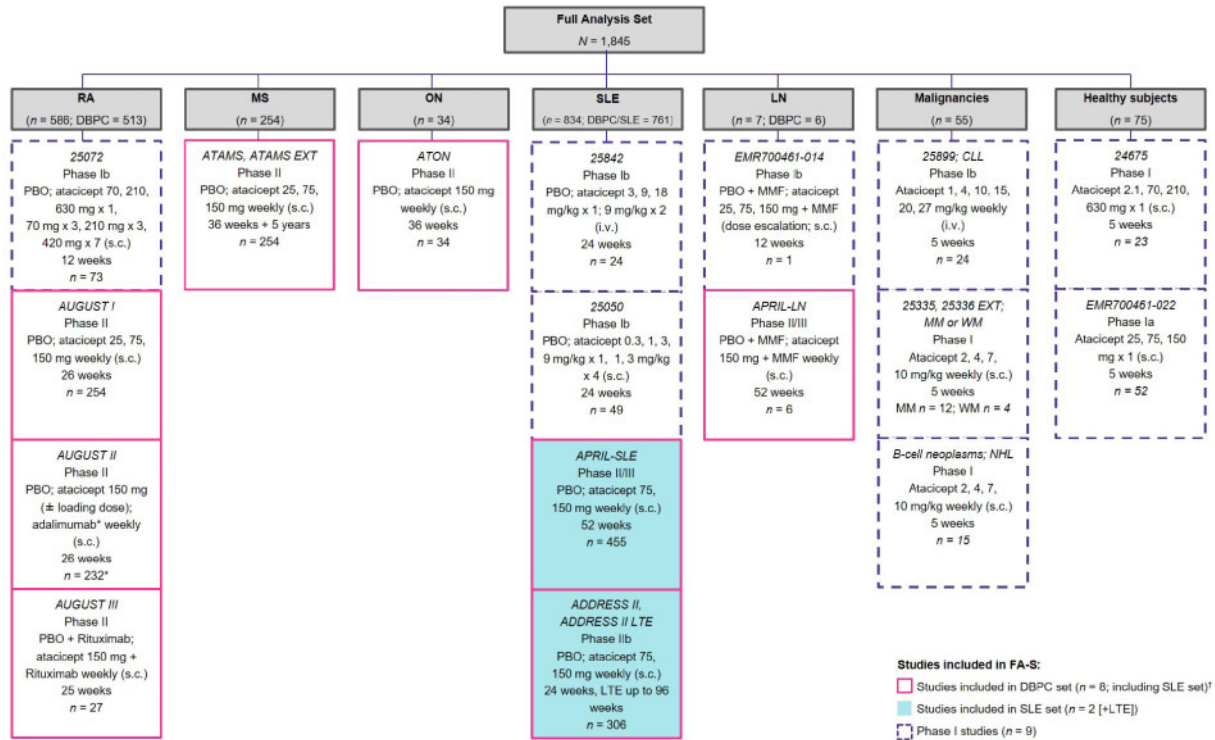
Data sets

Analyses were based on three separate pooled data sets to analyse all AEs (safety data) from all patients in the data set who were exposed to placebo or atacept during the studies: (i) DBPC set, comprising safety data from eight atacept Phase II or II/III DBPC studies conducted to date [not including long-term extension studies (LTEs)] [14, 15, 21–23, 25–27]; (ii) full analysis (FA) set, comprising safety data from all 17 clinical studies with atacept, including those belonging to the DBPC set [14–30]; and (iii) SLE set, comprising safety data from the APRIL-SLE and ADDRESS II studies [14, 15, 28].

Endpoints and assessments

Key safety endpoints analysed in the DBPC set included the overall incidence of AEs of special interest (AESI),

Fig. 1 Study population



*Patients treated with adalimumab (n=79) were not included in this analysis; †Extensions were not included within the DBPC set. RA studies: 25 072 [24], AUGUST I [21], AUGUST II [22], AUGUST III [23]. MS studies: ATAMS and ATAMS EXT [25]. ON study: ATON [27]. SLE studies: 25 842 [30], 25 050 [29], APRIL-SLE [14], ADDRESS II and ADDRESS II LTE [15]. LN studies: EMR700461-014 (not published); APRIL-LN [26]. Studies in malignancies: 25 899 [19]; 25 335+25 336 EXT [20]; B-cell neoplasms [18]. Studies in healthy subjects: 24 675 [16, 17]; EMR700461-022 [17]. CLL: chronic lymphocytic leukaemia; DPBC: double-blind placebo-controlled; EXT: extension; LTE: long-term extension; MM: multiple myeloma; MS: multiple sclerosis; NHL: non-Hodgkin's lymphoma; ON: optic neuritis; PBO: placebo; WM, Waldenström's macroglobulinaemia.

TEAEs, serious AEs and TEAEs leading to treatment discontinuation. Pre-defined AESI categories were based on potential or theoretical risks and included infections, hypersensitivity and injection site reactions (ISRs), severe hypogammaglobulinaemia (IgG <3 g/l), cardiac events (cardiac arrhythmias, cardiac failure and ischaemic heart disorders), embolic and thromboembolic events, vestibular disorders, demyelinating disorders, malignant tumours, and depression and suicide ideation (Supplementary Appendix 1, available at *Rheumatology Advances in Practice* online). In the FA set, the overall number and causes of deaths and the exposure-adjusted mortality rates across the atacicept clinical trial programme were examined. In the SLE set, the association between changes from baseline in IgG levels and mature B-cell numbers and rates of serious and/or severe infection were assessed.

Statistical analysis

Analyses were performed using descriptive statistics for continuous variables or by using the frequency count and percentage for categorical data. The TEAEs, AESIs and mortality rates were adjusted by atacicept exposure. The

exposure-adjusted incidence rate (EAIR) in each treatment arm was defined as the ratio of the number of patients with an event to the sum of the duration of exposure to treatment of the patients up to the time of the first event or the end of observation (whichever occurred first) and was expressed as the rate per 100 patient-years. In patients with SLE, serious infections [defined by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as resulting in death or life-threatening] and/or severe infections [defined by the Common Terminology Criteria for Adverse Events as a significant impairment of function (Qualitative Toxicity Scale)] were analysed (as a combined term) per quartile of changes from baseline in the serum IgG levels and mature B-cell numbers.

Results

Study population (DBPC, FA and SLE sets)

The DBPC set included 1568 patients treated for a total of 841.4 patient-years (Table 1; SLE, 48.5%; LN, 0.4%;

TABLE 1 Baseline demographics and disease characteristics by disease indication (double-blind placebo-controlled set)

	SLE		LN		RA		MS		ON	
	Placebo n = 254	Atacept n = 507	Placebo n = 2	Atacept n = 4	Placebo n = 147	Atacept n = 366	Placebo n = 63	Atacept n = 191	Placebo n = 17	Atacept n = 17
Gender, n (%)										
Male	19 (7.5)	38 (7.5)	1 (50.0)	1 (25.0)	24 (16.3)	63 (17.2)	18 (28.6)	68 (35.6)	3 (17.6)	4 (23.5)
Female	235 (92.5)	469 (92.5)	1 (50.0)	3 (75.0)	123 (83.7)	303 (82.8)	45 (71.4)	123 (64.4)	14 (82.4)	13 (76.5)
Race, n (%)										
White	197 (77.6)	358 (70.6)	1 (50.0)	0 (0.0)	139 (94.6)	325 (89.0)	62 (98.4)	188 (98.4)	17 (100.0)	16 (94.1)
Black	8 (3.1)	23 (4.5)	1 (50.0)	3 (75.0)	0 (0.0)	13 (3.6)	1 (1.6)	2 (1.0)	0 (0.0)	0 (0.0)
Asian	36 (14.2)	89 (17.6)	0 (0.0)	1 (25.0)	1 (0.7)	11 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native American or Alaska Native	4 (1.6)	7 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (3.5)	30 (5.9)	0 (0.0)	0 (0.0)	7 (4.8)	16 (4.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (5.9)
Age, mean (s.d.), years	39.9 (12.5)	39.2 (11.9)	36.6 (25.9)	36.9 (11.3)	53.9 (11.3)	53.8 (11.9)	38.1 (10.5)	38.2 (9.7)	32.8 (7.1)	31.2 (10.2)
Weight, mean (s.d.), kg	68.8 (15.1)	68.5 (17.2)	88.7 (13.1)	82.9 (23.1)	74.2 (16.6)	74.4 (16.9)	69.2 (14.4)	72.6 (17.4)	71.2 (14.9)	68.3 (12.5)
Disease duration, mean (s.d.), years	5.9 (6.4)	6.4 (6.1)	1.6 (2.3)	1.1 (2.2)	10.3 (7.3)	10.6 (8.2)	4.4 (5.5)	4.1 (5.3)	0.03 (0.02)	0.02 (0.02)

MS: multiple sclerosis; ON: optic neuritis.

RA, 32.7%; MS, 16.2%; and ON, 2.2%). Of these, 483 patients (30.8%) received placebo, and 129 (8.2%), 384 (24.5%) and 572 (36.5%) received atacept 25, 75 and 150 mg, respectively. Baseline demographics were balanced across treatment arms within the same indication (Table 1) [14, 15, 21–23, 25–28]. The FA set included safety data from 1845 patients, including healthy volunteers (n = 75) [16, 17], patients enrolled in Phase I studies (B-cell malignancies, n = 55; and autoimmune diseases, n = 147) [18–20, 24, 29, 30] and patients in the LTEs of DBPC studies [25, 28]. The SLE set included 761 patients enrolled in Phase II/III studies; these patients were treated for a total of 652.4 patient-years. The treatment duration ranged from 24 to 52 weeks in the DBPC and SLE sets and from 4 to 260 weeks in the FA set (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Exposure-adjusted incidence of AESIs and TEAEs (DBPC set)

Treatment exposure was similar between the placebo and atacept 75 and 150 mg groups (278.25, 225.02 and 286.67 patient-years, respectively), but was lower in the atacept 25 mg group (51.48 patient-years) (Table 2). Treatment exposure was highest in patients with SLE and lowest in those with ON and LN (Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

Exposure-adjusted rates of AESI were assessed by treatment/dose (Table 2) and indication (Supplementary Table S2, available at *Rheumatology Advances in Practice* online). Infections were the most common treatment-emergent AESIs, and the EAIRs were generally higher with atacept than with placebo (128.65 vs 107.78 per 100 patient-years). However, EAIRs of serious and severe infections were low across all patients (7.93 and 4.29 per 100 patient-years, respectively), with no notable differences between atacept and placebo. Although the overall infection rates were highest with atacept 150 mg, serious and severe infection rates were comparable to those with atacept 75 mg. There was no notable increase in the rates of serious and severe infections with atacept vs placebo in patients with SLE, RA or ON. In patients with LN or MS, the numbers of serious and severe infections were higher with atacept than with placebo, but few patients presented with these events. Herpes zoster infections occurred infrequently overall [n = 42 (5.07 per 100 patient-years)], and rates were similar between atacept and placebo. These infections were most frequent in SLE patients (n = 20) and occurred at slightly lower rates in RA and MS patients.

Hypersensitivity reactions occurred more frequently with atacept vs placebo (19.40 vs 13.92 per 100 patient-years) but were mostly mild in severity. Hypersensitivity reactions were most frequent in patients with ON or LN and were similar among patients with MS, RA or SLE. One patient with SLE in the atacept 75 mg group was hospitalized for anaphylactic shock after a bee sting; however, the causality was determined

TABLE 2 Summary of exposure-adjusted incidence rate of adverse event of special interests and treatment-emergent adverse events by dose (double-blind placebo-controlled set)

	Placebo <i>n</i> = 483			Atacept			All subjects <i>n</i> = 1568
	25 mg <i>n</i> = 129	75 mg <i>n</i> = 384	150 mg <i>n</i> = 572	All doses <i>n</i> = 1085			
Exposure, patient-years	278.25	225.02	286.67	563.16	841.41		
Treatment-emergent AESIs, <i>n</i> (per 100 patient-years)							
Infections	211 [107.78 (95% CI: 94.17, 123.35)]	180 [118.67 (95% CI: 102.54, 137.33)]	281 [141.30 (95% CI: 125.71, 158.83)]	504 [128.65 (95% CI: 117.90, 140.39)]	715 [121.70 (95% CI: 113.10, 130.95)]		
Non-opportunistic infections	0 (0.0)	0 (0.0)	1 (0.35)	1 (0.18)	1 (0.12)		
Opportunistic infections	13 (4.73)	10 (4.50)	17 (6.06)	29 (5.24)	42 (5.07)		
Herpes zoster infections	9 (3.24)	11 (4.94)	16 (5.59)	27 (4.82)	36 (4.29)		
Severe infections	20 [7.26 (95% CI: 4.68, 11.25)]	23 [10.47 (95% CI: 6.96, 15.76)]	22 [7.71 (95% CI: 5.08, 11.71)]	46 (8.27 (95% CI: 6.19, 11.04)]	66 [7.93 (95% CI: 6.23, 10.10)]		
Serious ^a infections	37 (13.92)	40 (19.06)	55 (20.36)	103 (19.40)	140 (17.57)		
Hypersensitivity ^b	54 (20.86)	109 (63.02)	156 (72.43)	292 (67.91)	346 (50.23)		
Infection site reactions	0 (0.0)	2 (0.89)	4 (1.40)	6 (1.07)	6 (0.71)		
Severe hypogammaglobulinaemia (IgG <3 g/l)	18 (6.62)	23 (10.61)	25 (8.87)	59 (10.77)	77 (9.40)		
Cardiac arrhythmias ^b	13 (4.75)	19 (8.69)	20 (7.07)	47 (8.53)	60 (7.28)		
Other arrhythmias	0 (0.0)	3 (1.33)	3 (1.05)	9 (1.60)	9 (1.07)		
Atrial arrhythmias	5 (1.81)	4 (1.79)	6 (2.10)	10 (1.79)	15 (1.79)		
Ventricular arrhythmias	6 (2.17)	7 (3.13)	15 (5.28)	24 (4.30)	30 (3.60)		
Cardiac failure	11 (3.99)	13 (5.92)	11 (3.87)	27 (4.87)	38 (4.57)		
Ischaemic disease and coronary artery heart disorders ^b	11 (3.96)	6 (2.67)	9 (3.16)	16 (2.85)	27 (3.22)		
Embolic and thromboembolic events ^b	19 (7.01)	18 (8.30)	26 (9.26)	49 (8.94)	68 (8.30)		
Vestibular disorders ^b	1 (0.36)	0 (0.0)	5 (1.74)	6 (1.07)	7 (0.83)		
Demyelination ^b	14 (5.08)	8 (3.58)	11 (3.87)	22 (3.93)	36 (4.31)		
Depression ^b	0 (0.0)	1 (0.44)	3 (1.05)	5 (0.89)	5 (0.59)		
Malignant tumours ^b	51 (18.94)	51 (23.85)	61 (21.79)	127 (23.35)	178 (21.89)		
TEAEs, <i>n</i> (per 100 patient-years)	28 (10.23)	45 (20.88)	56 (20.04)	111 (20.34)	139 (16.96)		
Serious TEAE	30 (10.85)	30 (13.39)	46 (16.13)	90 (16.07)	120 (14.34)		
Severe TEAE							
Discontinuation due to TEAE							

^aIncluding some infections also classed as severe.

^bProgrammatically determined (crude results of the search) from a predefined list of MedDRA preferred terms according to the Standardized MedDRA Query (SMQ) or Customized MedDRA Query (CMQ) classification of the corresponding MedDRA version. AESI: adverse event of special interest; TEAE: treatment-emergent adverse event.

to be unrelated to atacept. Rates of ISRs were higher with atacept compared with placebo, with the highest incidence in the atacept 150 mg group. However, ISRs were mostly of mild ($n = 117$, 15.4%) or moderate ($n = 25$, 3.3%) intensity, with three severe ISRs (0.4%). The EAIRs of ISRs were highest in patients with MS, LN and ON.

Severe hypogammaglobulinaemia (IgG < 3 g/l) was infrequent across all treatment groups, occurring in two (0.5%) and four (0.7%) patients in the atacept 75 and 150 mg groups, respectively, and being limited to patients with SLE (0.4%), LN (75.0%) or MS (0.5%). All patients with LN received loading doses of MMF (≥ 1 g/day) and high-dose CSs (prednisone, up to 60 mg/day) before the administration of atacept.

The EAIRs of cardiac arrhythmias, cardiac failure and ischaemic heart disorders were higher with atacept vs placebo. The highest incidence of cardiac arrhythmias was seen in the atacept 25 mg group, and no evidence of an atacept dose effect was observed. The highest EAIR of cardiac failure was observed in the atacept 150 mg group (5.28 per 100 patient-years), and EAIRs of 3.90, 3.13 and 2.17 per 100 patient-years were observed with atacept 25 and 75 mg and placebo, respectively. Analysis of these data by disease indication showed that cardiac arrhythmia rates were higher with atacept than with placebo in patients with MS or RA, but were similar between atacept and placebo in SLE patients. Ischaemic heart disorders were most common with atacept 25 (5.91 per 100 patient-years) and 75 mg (5.92 per 100 patient-years) in the overall DBPC set and were more frequent with atacept vs placebo in patients with RA (4.80 vs 1.62 per 100 patient-years). Embolic and thromboembolic events were more frequently reported in placebo-treated patients vs atacept-treated patients (3.96 vs 2.85 per 100 patient-years), with the difference being most pronounced in patients with LN or MS.

The incidence of vestibular disorders was 8.94 vs 7.01 per 100 patient-years with atacept (all doses) vs placebo, without evidence of an atacept dose effect. Seven out of 1568 patients experienced a demyelination event, with a higher incidence being observed with atacept than with placebo (1.07 vs 0.36 per 100 patient-years). Demyelination was observed only in patients with MS or ON and in a single patient with RA, for whom the demyelination event was unconfirmed.

Malignant or unspecified tumours were reported in a total of five (0.32%) atacept-treated patients across the SLE ($n = 2$), RA ($n = 2$) and MS ($n = 1$) groups, and no cases were observed with placebo; of note, the study sample included considerably more atacept-treated than placebo-treated patients for these indications, and the overall exposure [sum of the duration of treatment of the patients (placebo or atacept) until first AE or end of observation] was lower in the placebo group (Supplementary Table 2, available at *Rheumatology Advances in Practice* online).

The EAIRs of depression were higher with placebo than with atacept (5.08 vs 3.93 per 100 patient-years); no cases of suicide ideation or suicidal behaviour were observed.

Serious TEAE rates were low overall and similar between atacept and placebo groups. In atacept-treated

patients, the highest EAIRs were observed in the 25 mg group and the lowest in the 150 mg group (30.02 and 21.79 per 100 patient-years, respectively); however, these results should be viewed with caution owing to the smaller number of patients and lower exposure in the 25 mg group. Rates of severe TEAEs were higher with atacept than with placebo but were similar across atacept dose groups (Table 2). Analysis of TEAEs by disease indication showed that serious TEAE rates were higher with atacept than with placebo only in patients with LN, RA and ON, and severe TEAEs were more commonly observed with atacept than with placebo in all five indications. Discontinuation of treatment owing to TEAEs was relatively infrequent, but was more common with atacept vs placebo (16.07 vs 10.85 per 100 patient-years) overall, with the highest rate being seen with atacept 25 mg (27.57 per 100 patient-years) owing to the relatively smaller exposure time in this treatment arm (Table 2). Unadjusted discontinuation rates owing to TEAEs with atacept were 10.9% with 25 mg, 7.8% with 75 mg and 8.0% with 150 mg. The TEAE-related discontinuations were most frequent in patients with LN and RA; in patients with SLE, there was no difference in discontinuation rates between atacept and placebo.

Most common TEAEs (unadjusted for exposure; DBPC set)

Infections and infestations were the most frequently reported TEAEs (45.6%), and frequencies were similar between atacept 75 mg (46.9%), 150 mg (49.1%) and placebo (43.7%), but lower with 25 mg (33.3%; Table 3). The most commonly reported infections and infestations across all patients were urinary tract infections (10.2%), upper respiratory tract infections (10.1%), and nasopharyngitis (8.4%; Table 3; Supplementary Table S3, available at *Rheumatology Advances in Practice* online). The most frequently reported serious infection was pneumonia (atacept 75 mg, $n = 9$; atacept 150 mg, $n = 8$; and placebo, $n = 5$).

Mortality across the atacept trial programme (FA set)

Deaths that occurred across the atacept clinical trial programme are listed in Table 4. Eleven deaths occurred during treatment, and exposure-adjusted mortality rates per 100 patient-years (95% CI) were 3.60 (0.90, 14.38), 0.34 (0.05, 2.43) and 1.18 (0.49, 2.82) with atacept 25, 75 and 150 mg, respectively, and 0.44 (0.06, 3.12) with placebo (Table 5). One of the 11 deaths occurred after administration of a single dose of 25 mg atacept; this case is described in Supplementary Appendix 2, available at *Rheumatology Advances in Practice* online. Two additional patients died after the completion of atacept treatment: one patient with RA (9 months post-treatment; atacept 210 mg) and one patient with SLE (18 months post-treatment; atacept 150 mg). The exposure-adjusted mortality rate per 100 patient-years (95% CI) in patients with SLE was 0.78 (0.29, 2.07) across all atacept-treated patients and 1.45 (0.54–3.87) with atacept 150 mg; no

TABLE 3 Summary of treatment-emergent adverse events $\geq 5\%$ in any arm, by dose (double-blind placebo-controlled set)

System organ class Preferred term, n (%)	Placebo n = 483	Atacept				All subjects n = 1568
		25 mg n = 129	75 mg n = 384	150 mg n = 572	All doses n = 1085	
Infections and infestations	211 (43.7)	43 (33.3)	180 (46.9)	281 (49.1)	504 (46.5)	715 (45.6)
Urinary tract infection	49 (10.1)	8 (6.2)	46 (12.0)	57 (10.0)	111 (10.2)	160 (10.2)
Upper respiratory tract infection	41 (8.5)	4 (3.1)	41 (10.7)	72 (12.6)	117 (10.8)	158 (10.1)
Nasopharyngitis	33 (6.8)	8 (6.2)	35 (9.1)	55 (9.6)	98 (9.0)	131 (8.4)
Bronchitis	19 (3.9)	4 (3.1)	22 (5.7)	39 (6.8)	65 (6.0)	84 (5.4)
General disorders and administration site conditions	100 (20.7)	42 (32.6)	145 (37.8)	201 (35.1)	388 (35.8)	488 (31.1)
Injection site reactions	39 (8.1)	24 (18.6)	83 (21.6)	117 (20.5)	224 (20.6)	263 (16.8)
Influenza-like illness	22 (4.6)	15 (11.6)	15 (3.9)	11 (1.9)	41 (3.8)	63 (4.0)
Injection site erythema	3 (0.6)	2 (1.6)	15 (3.9)	29 (5.1)	46 (4.2)	49 (3.1)
Gastrointestinal disorders	97 (20.1)	20 (15.5)	98 (25.5)	129 (22.6)	247 (22.8)	344 (21.9)
Diarrhoea	27 (5.6)	5 (3.9)	27 (7.0)	38 (6.6)	70 (6.5)	97 (6.2)
Nausea	14 (2.9)	8 (6.2)	25 (6.5)	26 (4.5)	59 (5.4)	73 (4.7)
Nervous system disorders	92 (19.0)	28 (21.7)	83 (21.6)	100 (17.5)	211 (19.4)	303 (19.3)
Headache	56 (11.6)	21 (16.3)	56 (14.6)	63 (11.0)	140 (12.9)	196 (12.5)
Musculoskeletal and connective tissue disorders	86 (17.8)	21 (16.3)	70 (18.2)	105 (18.4)	196 (18.1)	282 (18.0)
Back pain	27 (5.6)	1 (0.8)	24 (6.3)	20 (3.5)	45 (4.1)	72 (4.6)
Respiratory, thoracic and mediastinal disorders	50 (10.4)	7 (5.4)	45 (11.7)	66 (11.5)	118 (10.9)	168 (10.7)
Cough	16 (3.3)	2 (1.6)	20 (5.2)	28 (4.9)	50 (4.6)	66 (4.2)

deaths occurred with weight-based atacept, atacept 75 mg or placebo.

Cardiac events were the most common cause of death in atacept-treated patients ($n=4$) and were deemed unrelated or unlikely to be related to treatment by the investigators.

Infections in SLE patients (SLE set)

Unadjusted rates of serious and/or severe infections (combined term for analysis) and infestations in atacept-treated patients were low and similar between the APRIL-SLE (19 of 295 patients; 6.4%) and ADDRESS II studies (including LTE; 13 of 206 patients; 6.3%). An analysis of serious and/or severe infections by quartile of serum IgG levels and changes in mature B-cell numbers from baseline showed no association between pharmacodynamic effects of atacept and infection rates; these findings were also confirmed across the full DBPC set. Severe hypogammaglobulinaemia (IgG <3 g/l) occurred in two atacept-treated patients with SLE (0.3% of all SLE patients; [Supplementary Table S2](#), available at *Rheumatology Advances in Practice* online) and was not associated with the development of infection.

Discussion

We conducted this integrated safety analysis of all 17 atacept clinical studies to date, including eight DBPC studies, to characterize the overall safety profile of

atacept in patients with autoimmune diseases. Similar to observations with other biologic agents that are frequently used to treat autoimmune diseases [31], the most commonly observed AEs with atacept were infections. This is not unexpected given the proposed B-cell-targeting mechanism of action of atacept, which has been shown to reduce Ig levels and B- and plasma-cell numbers [13, 14, 22, 25–27]. Our observations are also consistent with findings from clinical studies of other BLYS-targeting therapies [32–34]. It should be noted that although there was an increase in overall infection rates with atacept compared with placebo, the rates of serious and severe infections were not higher with atacept in patients with SLE, RA or ON. Furthermore, although infection rates appeared to be increased with atacept in patients with LN and MS, these observations should be viewed with caution given the overall low number of patients studied. Infection rates in patients with SLE enrolled in the ADDRESS II study were lower than those in patients enrolled in the APRIL-SLE study; this could be explained, in part, by the implementation of risk mitigation measures for ADDRESS II, following two pulmonary infections with fatal outcome in APRIL-SLE [14]. These mitigation measures, which included medical monitor reviews of patient screening data to confirm eligibility and up-to-date vaccinations against pneumococcus and seasonal influenza, have been and continue to be implemented in subsequent atacept studies [15].

Given the immunogenic potential of any biological or biotechnology-derived protein, hypersensitivity reactions

TABLE 4 Deaths registered across the atacicept programme (full analysis set)

Patient age and gender	Indication	Treatment dose	Event, days after first dose	Risk factors	Cause of death	Reference
Phase I, Ib and I/II studies						
60 years, male	RA	Atacicept 210 mg	286	Smoker	Lung cancer	Tak et al. (2008) [24]
80 years, male	CLL	Atacicept 2 mg/kg	41	Use of anti-coagulants (for atrial fibrillation); primary disease	Sepsis	Kofler et al. (2012) [19]
68 years, male	MM	Atacicept 7 mg/kg	74	Primary disease	Primary disease progression	Rossi et al. (2009) [20]
DBPC Phase II/III studies						
71 years, female	RA	Atacicept 25 mg	94	Vasculitis; CS use	Diverticular perforation	Genovese et al. (2011) [21]
70 years, female	RA	Atacicept 75 mg	149	Previous stroke; hypertension	Cardiorespiratory arrest	Genovese et al. (2011) [21]
67 years, male	RA	Atacicept 150 mg	55	History of cardiovascular disease; hypertension; diabetes	Sudden cardiac arrest	Van Vollenhoven et al. (2011) [22]
51 years, male	MS	Placebo	173	Chronic heart disease; coronary artery stenosis	Myocardial infarction	Kappos et al. (2014) [25]
22 years, male	SLE	Atacicept 150 mg	237	Digit ulcers secondary to scleroderma; endemic leptospirosis in country of residence	Acute respiratory failure; probable leptospirosis	Isenberg et al. (2015) [14]
30 years, female	SLE	Atacicept 150 mg	299	Primary disease; CS use	Pneumonia; pulmonary alveolar haemorrhage	Isenberg et al. (2015) [14]
61 years, female	SLE	Atacicept 150 mg	695	Advanced primary disease	Multi-organ failure	Isenberg et al. (2015) [14]
33 years, female	LN	Atacicept 25 mg	1	Smoker; hypercholesterolaemia; primary disease; chronic ischaemic heart disease	Acute myocardial infarction	see Supplementary Appendix 2 , available at <i>Rheumatology Advances in Practice</i> online
32 years, female	SLE	Atacicept 150 mg	563	Primary disease; NSAID (COX2 inhibitor: meloxicam)	Thrombotic stroke	–
56 years, female	SLE	Atacicept 150 mg	368	NSAID (COX2 inhibitor: aceclofenac)	Unknown	–

CLL: chronic lymphocytic leukaemia; DBPC: double-blind placebo-controlled; MM: multiple myeloma; MS: multiple sclerosis.

TABLE 5 Exposure-adjusted mortality rates in patients treated with placebo or atacept 25, 75 or 150 mg^a

	Placebo <i>n</i> = 431	Atacept 25 mg <i>n</i> = 130	Atacept 75 mg <i>n</i> = 384	Atacept 150 mg <i>n</i> = 677
Exposure, patient-years	227.68	55.63	291.66	425.26
Deaths, <i>n</i>	1	2	1	5
Exposure-adjusted mortality rate, per 100 patient-years (95% CI)	0.44 (0.06, 3.12)	3.60 (0.90, 14.38)	0.34 (0.05, 2.43)	1.18 (0.49, 2.82)

^aStudies with single or multiple ascending doses of atacept (*n* = 111) and weight-based atacept (*n* = 112) were not included for this analysis (two deaths occurred in studies of weight-based atacept).

and ISRs were of special interest. As anticipated, exposure-adjusted hypersensitivity and ISRs were more frequent with atacept than placebo. The highest frequencies were in patients treated with atacept 150 mg, but most reactions were of mild to moderate intensity, with only a single case of anaphylaxis related to a bee sting, and no fatal reactions.

Hypogammaglobulinaemia was defined as another AE of particular interest, based on outcomes of the Phase II/III DBPC APRIL-LN study (NCT00573157), which was terminated early following an unexpected decline in IgG, together with several serious infections. However, analysis suggested that these events might have been attributable to factors other than atacept treatment, because the reduction in serum IgG levels began 2 weeks before atacept treatment, after the initiation or dose increase of MMF and CSs [26, 35]. This is consistent with a report by Broeders *et al.* [36], which showed that hypogammaglobulinaemia is common in renal transplant patients who are treated with MMF and CSs. The analysis of the pooled DBPC data in this report showed a low incidence of severe hypogammaglobulinaemia with atacept (*n* = 6 patients; 0.4%). Additionally, our analysis of serious and/or severe infections occurring in patients with SLE enrolled in the APRIL-SLE, ADDRESS II and ADDRESS II LTE studies showed no apparent association between reduced serum IgG and mature B-cell levels with serious and severe infection rates.

Although the incidence of malignancies was numerically higher with atacept than with placebo, rates were overall low and appeared similar to the background rate of malignancies in SLE patients [37] and to rates reported with belimumab, based on 7 years of cumulative exposure data in SLE patients [38]. The analysed sample included considerably more atacept-treated than placebo-treated patients, and the imbalance in patient numbers might therefore account for the numerical difference in malignancies.

Across all patients (FA set), the number of reported deaths was 13 (of 1845 patients in total), which is comparable to clinical studies of other BLYS- and/or APRIL-targeting agents [32, 33, 39]. Cardiac events were the most common cause of death across all atacept studies (*n* = 4 of 13 deaths) and were deemed unrelated or unlikely to be related to treatment. Analyses of the

pooled DBPC data showed that EAIRs of cardiac events were low overall, with moderate increases for atacept vs placebo observed only in patients with MS and RA. Despite evidence that patients with SLE are at an increased risk of cardiovascular disease [40], EAIRs of cardiac events observed in this analysis were lower in patients with SLE than in the other indications and were similar with atacept and placebo. Interestingly, BLYS and APRIL are expressed in human arteriosclerotic plaques, suggesting that they could be a negative prognostic factor in cardiovascular disease [41].

Implications for future studies in SLE patients

Long-term use of standard-of-care treatments for SLE, including CSs and immunosuppressants, is associated with adverse effects, including infection [42]; however, prolonged exposure to these agents is often unavoidable owing to the chronic nature of the disease [43]. Thus, there is a need for novel targeted therapies that not only provide greater efficacy, but also have a safety profile that is conducive to chronic use.

Although none of the atacept studies to date has met its primary endpoint, clinical efficacy was demonstrated with atacept 150 mg in two large Phase II/III SLE studies with different study designs (Supplementary Table S5, available at *Rheumatology Advances in Practice* online). In the APRIL-SLE study, atacept 150 mg led to significant treatment benefits, with reduced flare rates and delayed time to the first flare over placebo (*post hoc* analysis of the discontinued arm) [14], and Gordon *et al.* [13] demonstrated that increased atacept exposure associated with the 150 mg dose led to greater reductions in Ig levels and B-cell numbers (pharmacodynamic effects), without a significant increase in hypogammaglobulinemia or infection rates. In the ADDRESS II study, atacept 150 mg showed significant treatment benefit over placebo in patients who had HDA at screening across different efficacy endpoints, and confirmed the consistent pharmacodynamic effects of atacept treatment [15, 28, 44]. Furthermore, no clinically meaningful differences in safety data were observed between the modified intention-to-treat and the HDA populations in ADDRESS II [15]. Taken together, these findings support treatment of HDA patients with SLE with atacept 150 mg in future studies [13–15].

The present analysis describes the EAIRs of most TEAEs in atacicept-treated patients. There was no consistent association with atacicept dose and cardiac arrhythmias, serious and severe infections, vestibular disorders, depression or malignant and unspecified tumours. By clarifying the frequency and severity of the potential risks associated with atacicept, this analysis provides a foundation for further investigation of the potential benefits of atacicept in SLE and other serious autoimmune diseases, while continuing to implement risk mitigation measures.

Study limitations

Limitations of this integrated analysis include the differing designs and patient populations of the studies included. In addition, overall patient numbers varied considerably by disease and dose, and sample sizes were small in some indications. However, in the DBPC set, atacicept was investigated in 150–500 patients for each autoimmune indication (excluding ON and LN) and ~130–570 patients for each dose.

Conclusion

In conclusion, the outcomes of this integrated analysis of safety data from >1800 subjects support further development and evaluation of atacicept in selected patients for whom the potential benefits might outweigh the risks, with measures to minimize infection-related risks associated with B-cell-targeting therapies.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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