Atacicept – It's Not Over Until The Wolf-Lady Sings [or maybe howls]

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Conflict of interest statement:

Dr Lin works for Vera Therapeutics.

Professor Isenberg has consulted for Eli Lilly, Amgen, Astra Zeneca, Merck Serono, Vera Therapeutics and Servier. The honoraria offered are passed on to a local charity.

Data access statement:

Reasonable requests to review the data referred to in this article are welcome.

Although the Federal Drug Administration [FDA] recently approved anifrolumab for use in patients with systemic lupus erythematosus [SLE], few biologics have been approved for this disease, compared to the many available for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Benlysta, which blocks the B-cell activity factor BAFF [B-cell activating factor of the tumour necrosis family], was approved for SLE by the FDA in March 2011, but no other monoclonal antibodies were approved in the next decade. Rituximab, which blocks CD20, while allowed by the National Health Service in the United Kingdom [August 2013] and recommended in the guidelines of both the American College of Rheumatology [1] and the European League Against Rheumatism [2] for lupus nephritis, is not formally approved by the FDA. Telitacicept which blocks B-lymphocyte stimulation [BLyS] and a proliferation-induced antigen [APRIL] received National Medical Products Association [NMPA] approval in China in 2021 for the treatment of active SLE. Nevertheless more effective treatment options are required for SLE.

Several monoclonal antibodies e.g. tabalumab , epratuzumab , ustekinumab having met their end points in phase II clinical trials subsequently failed to achieve their primary end points in phase III trials.

Atacicept impacts on B cell and plasma cell growth and differentiation, but has been searching for the right disease indication to show its utility. Atacicept reduces B lymphocyte numbers and immunoglobulin levels [3]. In its initial flare prevention Phase II/III study [APRIL-SLE], encouraging serological results, notably reductions in anti-dsDNA antibodies and rise in C3 levels, occurred but did not meet the primary end point in the intention to treat population [n = 401] [9]. The trial was foreshortened by the safety committee's decision to suspend the higher dose arm [150mg] when two patients died, including one from leptospirosis in Manila. This was an unfortunate decision as many clinical trials, using biologic or other novel drugs in patients with lupus, record a small number of deaths without the safety committee intervening. Thus, in the phase II trial of voclosporin, 11 deaths were recorded [5] which neither stopped this trial, nor the subsequent successful phase III trial proceeding. Encouragingly, among those patients who did receive the atacicept 150mg dose, a beneficial effect compared to placebo [OR: 0.48; p =0.02 and time to first flare [HR: 056, p = 0.09] was noted. A subsequent integrated safety

analysis of 17 randomized, placebo-controlled trials showed that in the SLE and double-blind placebo-controlled data sets, pharmacodynamic effects of atacicept were not associated with increased serious infection rates. Across all indications, exposure-adjusted mortality rates were similar between atacicept and placebo [6]. A post-hoc analysis of the phase II/III APRIL-SLE study had previously demonstrated a close relationship between the concentrations of atacicept, reduced immunoglobulin levels and flare rates suggesting that baseline biomarkers, notably elevated levels of BLyS and APRIL, could identify patients most likely to benefit from atacicept .

In a 24-week multi-centre randomised double-blind placebo-controlled phase IIb study [ADDRESS II] in SLE [7] using the SLE responder index 4 [SRI-4] at week 24 as the primary end point, severe risk of disease flare was reduced with atacicept therapy in both the intention to treat group [n = 306] and in those patients with high levels of disease activity. The risk of serious adverse events and serious or severe infections was not increased with atacicept compared to placebo. Data from this trial were used to study three treat-to-target end points [8] low disease activity [defined as SLEDAI-2K </= 2], low disease activity state [LLDAS] and remission [judged by a clinical SLEDAI-2K of 0 prednisolone $\leq$5mg per day and physicians global assessment of $\leq$0.5] which were shown to be more stringent than the SRI-4 and SRI-6 responses attained in the high disease activity group.

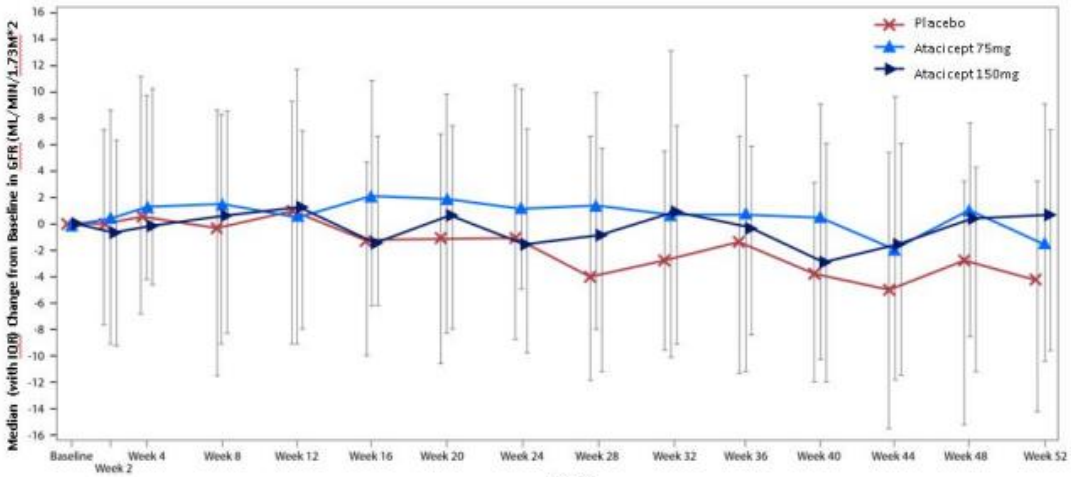
In a safety and clinical activity long-term extension study of ADDRESS-II [9] treatment, emergent adverse events were similar across the placebo and lower [75mg] and higher dose [150mg] atacicept groups. No new safety signals or deaths were observed. The reduction in the incidence of severe flares and longer time to first severe flare observed in the ADDRESS-II core study [11] was maintained in the long-term extension study. Importantly, few patients in the groups who switched from placebo to atacicept 150 experienced new severe flares following the switch.

A caveat in the studies described above is that they were all focused on patients with musculoskeletal and skin disease. A brief attempt to study atacicept (150mg administer twice weekly) in patients with renal lupus (APRIL-LN), was halted [10] because three out of four patients given the combination of high-dose corticosteroids, MMF, and then atacicept, suffered severe chest infections. None died, but in each patient their IgG levels decreased

profoundly. A subsequent review of the data indicated the reductions in immunoglobulin levels were associated with the high dose corticosteroids and mycophenolate, not the atacicept. Very little data has been published about the potential use of atacicept in patients with lupus nephritis.

In APRIL-SLE, patients with moderate to severe glomerulonephritis were excluded, [defined by either of the following: urinary protein/creatinine ratio (UPCR) >1 mg/mg and/or hematuria or a significant renal impairment as defined by estimated glomerular filtration rate (eGFR)]. However, some patients with 'low grade' nephritis were studied. Among this subset of patients, 111 patients in the placebo group, 112 and 150 patients in the atacicept 75 mg/150mg group respectively completed 52 weeks of treatment. The eGFR time course was stable for the atacicept groups compared to a 4.4% decline in the placebo group from baseline at week 52 (Figure 1 and Table 1). UPCR from baseline at week 52 declined in the atacicept groups and increased in the placebo group. Results from this study suggest the potential for improved renal function with atacicept. Vera, atacicept's sponsor, received FDA feedback on its LN development plans, and will begin a phase III study evaluating atacicept 150 mg administered weekly compared to placebo. Thus the time is coming when we will finally discover if atacicept can be used to treat renal lupus successfully.

Figure 1



Placebo	N=153	148	149	147	142	143	139	138	131	128	128	123	115	110	110
Atacicept 75mg	N=155	147	143	139	136	133	132	125	121	123	116	116	113	111	111
Atacicept 150mg	N=144	141	141	127	122	116	107	100	97	90	85	78	68	70	62

Median Change from Baseline in eGFR

Table 1

Variable	Placebo	Atacicept 75 mg	Atacicept 150 mg
eGFR (mL/min)	n=110	n=111	n=62[b]
median	-4.35	-1.49	0.57
UPCR (mg/mg)	n=108	n=108	n=63
median	6.29	-6.27	-12.72
UPCR (mg/mg)[a]	n=12	n=15	n=8
median	26.11	-54.42	-12.15

eGFR=estimated glomerular filtration rate; UPCR=urinary protein/creatinine ratio
a Among patients with screening UPCR ≥0.2 mg/mg
b Enrollment in the atacicept 150 mg arm was discontinued prematurely (described in Isenberg et al., 2015)

Percent Median Change in Baseline of eGFR and Proteinuria at Week 52

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