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Article Type: Drug Profile

Epratuzumab for the treatment of systemic lupus erythematosus

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease. There are three drugs licensed for the treatment of lupus: corticosteroids, hydroxychloroquine and belimumab. Immunosuppressants such as azathioprine, methotrexate and mycophenolate are also used. Despite these treatments there is still considerable morbidity. New treatments are needed for the management of active lupus. Epratuzumab a humanized IgG1 monoclonal antibody that targets CD22 resulting in selective B cell modulation that has been considered a potential treatment for SLE.

Areas covered: Summary of the relevant pathogenesis and disease activity measurements used in SLE patients, current treatments and unmet needs in SLE, pharmacokinetics and pharmacodynamics of epratuzumab therapy, and a summary of the 7 clinical trials that have investigated the efficacy and safety of epratuzumab in SLE.

Expert commentary: It is not clear why trials have failed to demonstrate efficacy but high placebo response rates from optimisation of standard of care and a sub-optimal dosing regimen may have played a role. Post-hoc analysis suggested that there may be subgroups that did respond, such as anti-SSA positive patients with features of Sjogren's syndrome. Further research is needed to explore this and other potential sub-groups that might respond.

Keywords: B cell modulation, BILAG, BICLA, CD22, disease activity, epratuzumab, monoclonal antibody, lupus, outcome, response, Sjogren's syndrome, SLEDAI-2K, treatment

Epratuzumab for the treatment of Systemic Lupus Erythematosus

1. Search criteria

MEDLINE and PubMed databases where searched using the keywords epratuzumab, systemic lupus erythematosus (SLE) and CD22. All clinical papers were selected and included in this review. For mechanistic papers recent up to date review articles were selected along with a few of the principle original papers.

2. Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease. The estimated incidence and prevalence of SLE in the UK is 4.91/ 100,000 and 97.03/100,000 respectively (1) and in the USA 5.5/100,000 and 72.8/100,00 respectively (2). SLE is more common in females than in males with a ratio of 8-15:1 and tends to present between the second and fifth decades (2). SLE is most prevalent in people of African, South Asian and Chinese descent (1,3).

SLE is a clinical diagnosis that should be associated with at least one serological abnormality that supports an underlying autoimmune immune-complex mediated pathological process (4). The Systemic Lupus International Collaborating Clinics (SLICC) classification criteria can be used as a validated objective classification tool in research and clinical practice (5). The American College of Rheumatology classification criteria for SLE has been used for longer in lupus research, contains less items and is less sensitive but is a bit more specific (4).

2.1 Pathogenesis of SLE

There are numerous genetic and environmental factors associated with the development of lupus (6-8). SLE is thought to be primarily a B-cell mediated disease. Inappropriate immune activation leads to the expansion of autoreactive B cells that develop into plasma cells producing many autoantibodies including anti-DNA, anti-Ro, and antiphospholipid antibodies. Defective immune clearance of apoptotic cells leading to exposure of intra-cellular antigens to the immune system, complement

deficiency (C1q, C2, C4) (9) and mannose binding lectin (MBL) deficiency (10). Autoantibodies causing immune complex disease trigger complement activation and inflammatory cytokine release leading to the inflammatory features of SLE (11,12). The autoreactive B cells also have a role in activating antigen presenting cells (APCs), producing inflammatory cytokines and regulating T cell activation and expansion (6).

2.2 Measuring disease activity in SLE

SLE is a heterogeneous disease affecting one or multiple organ systems. Three patterns of disease have been reported: acute disease flare, more chronic active disease and quiescence (13). Clinical assessment of disease activity may be confounded by chronic organ damage from SLE, co-morbidities such as fibromyalgia and adverse drug reactions (4). Disease activity indices have been developed for use in clinical trials and observational studies (14).

The British Isles Lupus Assessment Group Disease Activity (BILAG) index (15) and its revision the BILAG-2004 index (16,17) record disease activity in the last 4 weeks. The scoring is based on an intention to treat principle derived by consensus. Disease activity in each system is attributed a letter (categorical score) corresponding to the level of disease activity. Score A is assigned to severe disease activity requiring increases in prednisone to >20 mg daily and/or addition of immunosuppressive agents. Score B is assigned to less active disease needing only low dose prednisolone and/or symptomatic treatment with non-steroidal anti-inflammatory drugs or antimalarials. Score C is assigned to mild or improving features requiring only symptomatic therapy. Score D is assigned to previous disease activity in a system with no current disease activity. Score E indicates no prior or current disease activity in the system. The BILAG-2004 revision used similar scoring principles as the original BILAG index but changed the grading of severe disease activity items if they were improving (14). There were 8 systems in the original BILAG index (15); constitutional, mucocutaneous, neurological, musculoskeletal, cardiovascular/respiratory, vasculitis, renal and haematological. In the BILAG-2004 index the vasculitic features were moved into individual organ systems and gastrointestinal and ophthalmologic systems were added resulting in a total of 9

systems. Many of the items in each system, their glossary definitions and the option for numerical scoring were updated in this revision (16,17). The classic BILAG and BILAG-2004 indices are summarised in table 1.

The SLE Disease Activity Index 2000 (SLEDAI-2K) is another validated global measure of SLE disease activity (18). It provides a weighted score for each of 24 clinical, haematological and serological items originally over a recall period of 10 days but was more recently validated to be used over 4 weeks to give a numerical score indicating overall disease activity (14). The components and scoring of SLEDAI-2K are summarised in table 1. The physician's global assessment (PGA) is used in composite responder indices. The PGA score is determined by the overall disease activity score given by the assessing doctor using a visual analogue scale (14). More recent studies have used the composite BILAG-based combined lupus assessment (BICLA). It was developed by an expert panel and combines the BILAG-2004 index, SLEDAI-2K and PGA (14). A BICLA responder is defined as a patient meeting predefined criteria for BILAG-2004 index improvement with no worsening of total SLEDAI-2K score or PGA and no treatment failure. This is similar to the SLE responder index (SRI) used in the belimumab trials (19,20) which requires improvement in the SELENA version of SLEDAI (4), with no significant worsening in the BILAG index and no worsening in the PGA (14). The BICLA and original SRI are summarised in table 2.

2.3 Current therapeutic approaches and unmet needs

The current licensed pharmacological treatments for SLE are; hydroxychloroquine, corticosteroids and belimumab (4). Immunosuppressants such as azathioprine, methotrexate, mycophenolate mofetil, ciclosporin, tacrolimus and cyclophosphamide are used (4). Belimumab is the only biological therapy to be licensed following 2 successful phase III trials (19,20). Rituximab has shown efficacy in open label studies and is used in refractory lupus despite failing in phase 3 clinical trials (4).

Despite significant advances in care with standard therapy a significant number of patients have flares or chronic moderate activity that are treated with corticosteroids and immunosuppressants that contribute to end organ damage and risk of infection,

atherosclerosis and premature death. There is plenty of scope for the development of more targeted and effective therapies.

2.4 CD22

CD22 is a 135-kD type I transmembrane sialoglyco-protein of the Ig superfamily found specifically on B cells (21). CD22 is thought to play an important role in the modulation of B cells and humoral immunity. CD22 acts as an inhibitory co-receptor to the B-cell receptor (BCR) causing BCR induced cell death (21). When CD22 and BCR are cross-linked by antigen triggers, CD22 undergoes phosphorylation causing downstream reduction of BCR calcium signalling (22) and down regulation of BCR signalling ultimately resulting in BCR induced cell death and reduced overall survival of B transformed cells or diminished proliferation of B cells from patients with SLE (21,23). Studies of CD22 deficient mice show increased BCR calcium signalling response to BCR ligation, implying that CD22 inhibits BCR signalling by reducing calcium efflux (24) possibly via potentiating plasma membrane calcium-ATPase activity (25). Because of the B cell specificity of CD22 and the inhibitory effects of stimulating CD22, it has been considered a prime therapeutic target in B cell mediated autoimmunity such as SLE as well as for non-Hodgkin's lymphoma (26).

3. Epratuzumab structure and chemistry

Epratuzumab is a humanized CD22 targeted IgG1 monoclonal antibody derived from the murine IG2a monoclonal antibody LL2, which binds to extracellular domain of CD22 (27). Epratuzumab has low immunogenicity as only 5-10% of the molecule consists of murine sequence the rest being human (28). Like many monoclonal antibodies it was first developed as a treatment for lymphoma (27). Epratuzumab is given as an IV infusion typically with an infusion time between 30 – 60 minutes. Immunomedics Inc. developed epratuzumab originally for use in oncology (26,27) and licensed Union Chimique Belge (UCB) to develop epratuzumab for use in autoimmune diseases such as SLE.

3.1 Epratuzumab pharmacodynamics

Epratuzumab is thought to work primarily via the immunomodulation of B cells via its action on CD22 and subsequent effects on BCR signalling, surface receptor expression, cytokine expression, potential reduction in plasma cell generation as well as effects on cell adhesion and migration as discussed below (22,28-33). The main mechanisms of action are summarised in figure 1.

Epratuzumab activates the regulatory functions of CD22 by initiating CD22 phosphorylation (28). It induces the internalisation of CD22 and of CD79α, which is a part of the BCR complex (22), hence disrupting BCR signalling. Epratuzumab down regulates CD19, CD79β and CD21 from the cell surface via trogocytosis (29). Trogocytosis is the process by which cell surface receptors are transfer from one cell to another, in this case to phagocytic cells such as macrophages. CD19 has been implicated in the pathogenesis of SLE with certain polymorphisms associated with the predisposition to SLE (34). CD19 loss increases the BCR threshold and further reduces BCR signalling (35).

Epratuzumab inhibits the production of the pro-inflammatory cytokines TNF and IL-6 whilst preserving production of the anti-inflammatory cytokine IL-10 (30,36). Therefore epratuzumab should change the overall balance of pro- versus anti-inflammatory cytokines.

Another effect of epratuzumab is to alter the B cell migratory capacity by modulating cell adhesion molecules. Epratuzumab has been shown to down regulate CD62L and β7 integrin whilst up regulating β1 integrin and increasing B cell migration to CXCL12 (31). CD62L and β7 integrin are adhesion molecules used for lymphocyte recruitment to inflamed tissues and mucosa respectively. By down regulating these molecules pathological B cells may be impeded in their recruitment to sites of inflammation. CXCL12 is a chemokine produced by bone marrow and along with β1 integrin are used in the recruitment of lymphocytes into the bone marrow (32). One effect of this up regulation could be that naïve B cells become trapped in the bone marrow preventing them from fully differentiating in secondary lymphoid organs.

In contrast to Rituximab in vitro studies into the mechanism of epratuzumab show no complement dependent cytotoxicity (CDC) and very small antibody dependent

cellular cytotoxicity (ADCC) (37). Interestingly data from 2 phase III clinical trials (EMBODY 1 and EMBODY 2, see below) show a total B cell reduction of 30-40% with epratuzumab (33). This can be explained by the fact that B-cells require BCR activation for maturation and survival (38). Therefore with epratuzumab reducing BCR signalling via CD19, CD79β/ CD79α and CD21 internalisation/ trogocytosis and CD22 phosphorylation less B cells mature and survive causing a reduction in overall B cell numbers. In particular it is the CD27negative B cell subset that is most depleted due to the fact that CD22 is more highly expressed in this subset (31).

In summary epratuzumab works by a process of immunomodulation of B cells by enhancing the normal inhibitory function of CD22 on the BCR (39) with less than 50% B cell depletion, as opposed to ADC and ADCC associated with rituximab which targets CD20 and causes marked B cell depletion. The advantages of epratuzumab over a B cell depleting drug such as rituximab could be disease amelioration without potentially dangerous immunosuppressive effects. For example rituximab has been linked with progressive multifocal leukoencephalopathy (PML), a fatal infection of the central nervous due to JC virus (40), although this remains a rare complication and occurs with other monoclonal antibodies and cytotoxic agents (41).

3.2 Epratuzumab pharmacokinetics

Pharmacokinetic results from the original non-Hodgkin's lymphoma trials suggested that the serum half-life of epratuzumab is around 23 days, similar to the half-life of human IgG (26,42). In the initial clinical trial of epratuzumab in SLE serum concentrations of epratuzumab were measured up to week 18 (12 weeks post last infusion). Concentrations fell with time since the last infusion but were measurable in all patients at 10 weeks (4 weeks post last infusion) and continued to be detected in some patients at 18 weeks (12 weeks post last infusion) (43).

4. Clinical efficacy

To date there have been 7 clinical trials (1 phase IIa open label trial, 1 phase I/II, 3 phase IIb and 2 phase III randomised controlled trials (RCTs)) and 3 extended open

label studies (results of ALLEVIATE and EMBLEM extensions are published, EMBODY extension unpublished (ClinicalTrials.gov Identifier: NCT01408576)) looking at the efficacy, safety and pharmacokinetics of epratuzumab in SLE. In total 2167 patients were recruited into these trials with a total of 1313 patients receiving epratuzumab as part of a RCT and 57 patients receiving epratuzumab as part of an open label trial (14 patients received epratuzumab in the initial open label trial and 43 patients switched from placebo to epratuzumab in an open label extension). The primary endpoint in all trials (with the exception of the Japanese phase I/II study) has involved reduction in SLE disease activity defined either a BILAG or BICLA index responder as described earlier and in tables 1 and 2. All studies have also looked at drug safety outcomes.

4.1 Initial open label trial (43)

The initial open label, non-randomised, single centre clinical trial of epratuzumab was conducted with 14 patients with the aim of obtaining preliminary evidence of its therapeutic effect and drug safety in SLE. Study outcomes were BILAG score before and after treatment, adverse events and serological measurements. Inclusion and exclusion criteria are summarised in table 3 and the results in table 4. In total 14 patients were entered; all of Caucasian ethnicity (13 females and 1 male) with an age range 23-53 years old (median age 40). All patients had a BILAG score of between 6-12 (median 10 using the original ad-hoc numerical score (44)). Patients received 4 doses of 360 mg/m^2 at 2 weekly intervals. Epratuzumab was administered along with paracetamol and an antihistamine as premedication. Patients were followed up at 6, 10, 18 and 32 weeks. Intravenous (IV), intramuscular (IM), intra-articular (IA) and high dose corticosteroids along with cyclophosphamide were not allowed within 4 weeks of study entry. Low dose background therapy was allowed as long as there were no dose adjustments within 4 weeks of study entry.

The majority of patients completed the trial with 12 of 14 patients receiving all 4 infusions. Statistically significant improvements in BILAG scores were observed with 77%, 71% and 38% of patients showing a 50% or more improvement in classic BILAG score at 6, 10 and 18 weeks respectively. All BILAG organ systems showed

some disease activity improvement in response to epratuzumab apart from hematologic where 2 patients showed worsening of disease activity and no patients showing improvement. At week 18 only 3 patients (21%) had BILAG deterioration in at least one organ system.

Adverse events (AEs) were reported in 10 patients; 6 had mild, short lasting infusion reactions such as sleepiness, flu like symptoms, tracheitis, arthralgia, myalgia, fever, nausea, headache and rash. Five patients developed infections such as otitis media, tonsillitis, cystitis, vaginal candidiasis and herpes zoster, that all resolved with appropriate treatment. There was one serious adverse event (SAE), which was thought to be unrelated to the drug and no deaths. Mean B cells were reduced by 35% post epratuzumab and this decrease was consistent at 32 weeks. There was no consistent effect on immunoglobulins, T cells, autoantibodies or C3 levels. There were no anti-human epratuzumab antibodies detected.

The limitations of this study were its small numbers, no control group or randomisation and no measurement of Health Related Quality of Life (HRQoL) or steroid sparing effects of epratuzumab. In conclusion this open label non-randomised study demonstrated that epratuzumab is a generally safe and well tolerated drug with some possible disease ameliorating effects in SLE.

4.2 Phase IIb trials: ALLEVIATE-1 and ALLEVIATE-2 (45,46)

ALLEVIATE-1 and ALLEVIATE-2 were 2 phase IIb multicentre, multinational, double blinded, placebo-controlled, randomised controlled trials, looking at the efficacy and safety of epratuzumab in SLE. Unfortunately due to drug supply shortages the trials were discontinued early and the data were combined for analysis. ALLEVIATE-1 and ALLEVIATE-2 studied patients with at least 1 BILAG A organ system and at least 2 BILAG B organ systems at baseline respectively.

Inclusion and exclusion criteria are summarised in table 3 and the results in table 4. In ALLEVIATE-1 patients had to have BILAG A disease ≥1 organ systems (excluding

renal and CNS). In ALLEVIATE-2 patients had to have BILAG B activity ≥2 organ systems.

In ALLEVIATE-1 patients were randomised to individualised standard of care (SOC) plus either epratuzumab 360mg/m^2 or epratuzumab 720mg/m^2 or placebo in a 1:1:1 ratio. In ALLEVIATE-2 patients were randomised to individualised SOC plus epratuzumab 360mg/m^2 or placebo in a 1:1 ratio. Assessments of disease severity using BILAG score were carried out every 4 weeks and were centrally graded by an independent blinded assessor. Patients were allowed to take background corticosteroids and immunosuppressants. If a disease flare occurred a protocol-driven corticosteroid regime was followed.

The primary end point was revised before the analysis was done and required BILAG response with no treatment failure at week 12 in the combined treatment groups from the two original trials. BILAG response was defined as all BILAG A scores reducing to B or lower and all BILAG B scores reducing to C or lower with no new BILAG A and less than 2 new BILAG B scores in other systems. Treatment failure was defined as new or increased use of oral corticosteroids or other immunosuppressants above baseline. Secondary endpoints were BILAG response at 24 and 36 weeks, time to initial BILAG response and total BILAG score at 12, 24 and 48 and time to first sustained BILAG response, physician global assessment (PGA), patient global assessment (PtGA) and health related quality of life (HRQoL) measured with short form 36 survey (SF-36). Safety endpoints and immunological endpoint were also analysed.

In total 90 patients were enrolled and randomised (36 in ALLEVIATE-1 and 54 in ALLEVIATE-2), with 37, 42 and 11 patients randomised to the placebo, epratuzumab 360mg/m^2 and epratuzumab 720mg/m^2 groups respectively. Baseline characteristics were generally comparable between groups with exception of some expected difference in the epratuzumab 720mg/m^2 group. This group had higher disease activity and higher background steroid use due to higher disease activity in patients in the ALLEVIATE-1 trial.

Due to premature discontinuation of the study a large number of patients did not complete the study as planned. In total 80% of patients in all groups were assessed at week 12 and over 60% were assessed at week 24.

The study failed to meet its primary outcome with there being no significant difference in BILAG response at week 12. Of the 74 patients who received 12 weeks of treatment 44.1%, 20.0% and 30.3% of patients were BILAG responders in the 360mg/m^2, 720mg/m^2 and placebo groups respectively (p=0.177 epratuzumab versus placebo) (45).

Of the secondary outcomes there was no significant difference in BILAG response at 24 and 36 weeks. There was no statistically significant difference in medium time to first initial BILAG response between the groups. Of exploratory outcomes, at 48 weeks median BILAG scores decreased from 12 to 4, 15 to 6 and 12 to 7.5 from baseline in the 360mg/m^2, 720mg/m^2 and placebo groups respectively. The overall change from baseline in total BILAG score at week 48 for all epratuzumab patients vs placebo was significant (p=0.028) (45).

The combined analysis showed a significant corticosteroid sparing effect of epratuzumab after post hoc adjustments for ethnicity, baseline immunosuppression and flare regime. At week 24 overall corticosteroid doses per patient were lower in both epratuzumab groups compared to placebo, seeing a reduction of 1051 mg (p=0.03 versus placebo) and 1973 mg (p=0.08 versus placebo) compared to placebo in the 360mg/m^2 and 720mg/m^2 groups respectively (46).

The number of patients who had an improvement in physician global assessment (PGA) and patient global assessment (PtGA) was generally higher in the epratuzumab groups compared to placebo, but this was not statistically significant. Looking at health related quality of life (HRQoL) there was improvement in 5 of the 8 domains of the short form 36 (SF-36) in patients receiving epratuzumab. These improved domains were bodily pain, social function, role emotional, mental health and vitality (the largest improvement being seen in vitality) (46).

The incidence of adverse events (AE) and serious adverse events (SAEs) were similar between all groups and there were no unexpected findings of concern and likely to be due to trial medication in the epratuzumab exposed patients. There was one drug unrelated death in the 720mg/m^2 group. The patient died of cerebral haemorrhage 16 weeks after the last dose. Of the 51 patients receiving epratuzumab 2 patients developed low level titres of human anti-human antibody (HAHA). Immunological studies showed a medium B-cell reduction of 31% and 52% from baseline in the 360mg/m^2 and 720mg/m^2 groups respectively. There were no changes in T cell numbers and immunoglobulin levels.

The limitations of this study are that due to early discontinuation the study was underpowered for the primary end point. Due to the relatively small numbers and as the exploratory analysis was not adjusted for multiple testing the results should be interpreted with caution. Overall the study points to some efficacy of epratuzumab on disease severity, corticosteroid sparing and HRQoL improvements and no concerns with drug safety.

4.3 ALLEVIATE open label extension trial (SL0006) (45,46)

ALLEVIATE patients at US sites were eligible for enrolment into the open label extension (SL0006) if they had benefitted from treatment in the randomised controlled trial and there were no safety concerns related to the administration of epratuzumab. The main objective was to assess the long-term safety and efficacy of an epratuzumab 360mg/m^2 maintenance regime of 12-week cycles (2 infusions on weeks 0 and 1 of each cycle). BILAG disease activity was assessed at 4 weekly intervals and 29 patients were recruited but 4 patients discontinued the study prematurely, 1 due to lack of efficacy and 3 due to SAEs.

There was a reduction in mean total BILAG score of 8.4 at entry to 7.2 at week 100. No new or unexpected AEs, SAEs or infections were reported. All 29 patients reported at least 1 AE with SAEs occurring in 10 patients. Corticosteroid sparing effects were observed with 77.9% of patients having reductions in corticosteroid dose and 40.7% stopping corticosteroids altogether. Improvement in HRQoL from

the ALLEVIATE baseline were maintained or improved in all SF-36 domains during SL0006.

4.4 Phase IIb trial: EMBLEM (47)

EMBLEM was a 12 week dose and regimen finding phase IIb, multicentre, multinational randomised controlled trial investigating the efficacy and safety of various epratuzumab doses in moderate to severe SLE. Inclusion and exclusion criteria are summarised in table 3 and the results in table 4. Inclusion criteria were similar to the ALLEVIATE studies with the addition of patients having to have a SLEDAI-2K total score of ≥ 6.

Patients were randomised to placebo or epratuzumab at the doses; 200mg cumulative dose (cd) (100mg every other week (EOW)), 800mg cd (400mg EOW), 2400mg cd (600mg weekly), 2400mg cd (1200mg EOW) and 3600mg cd (1800mg EOW) at a 1:1:1:1:1:1 ratio. Patients were given infusions between weeks 0 and 3. Clinically efficacy was assessed at weeks 4, 8 and 12.

The primary endpoint was the BICLA responder rate at week 12 according to this composite endpoint (14). In the study protocol steroids could be tapered at discretion of investigators. The study had multiple secondary endpoints looking at responder rate at 8 weeks, the individual disease severity scores at various time-points and corticosteroid usage. Various immunological parameters were also looked at as well as drug safety.

In total 227 patients underwent randomisation. Baseline characteristics were similar. Premature discontinuation occurred in 28 patients, most commonly due to lack of efficacy. The study failed to meet its primary outcome, with responder rates between all epratuzumab groups combined and placebo not being significant. In an exploratory paired analysis there was a statistically significant difference in responders in the epratuzumab 2400mg cd (600mg weekly), 2400mg cd (1200mg every other week) and combined 2400mg cd groups (p values 0.03, 0.07 and 0.02 versus placebo respectively) compared to placebo.

Looking at secondary outcomes there was no statistically significant difference in response rates between placebo and epratuzumab groups at weeks 8 and 12. Corticosteroid dose changes at week 12 compared to baseline were minimal.

In a post hoc exploratory analysis the epratuzumab 2400mg cd (600mg weekly) group had reductions in musculoskeletal, mucocutaneous, cardio-respiratory, neuropsychiatric, constitutional and renal BILAG systems compared to placebo. The epratuzumab 2400mg cd (1200mg EOW) showed BILAG system improvement in musculoskeletal, mucocutaneous and neuropsychiatric scores compared to placebo.

Laboratory studies showed that immunoglobulin levels stayed within normal limits. There was a moderate reduction in B-cell counts and CD22 expression in patients who received epratuzumab. The were no trends observed in complement and auto-antibody levels.

The EMBLEM study did not raise any new safety concerns. AEs and SAEs were similar across all groups and unrelated to epratuzumab dose. The most common AEs were headache, nausea, upper respiratory tract infection and urinary tract infection. There were no deaths.

In summary EMBLEM showed no overall efficacy of epratuzumab in the primary outcome however exploratory analysis showed a statically significant improvement in both epratuzumab 2400mg cd groups compared to placebo. Hence these dosing regimens were used in the phase III studies. EMBLEM flagged no new safety signals and demonstrated that epratuzumab is generally well tolerated. EMBLEM was the first trial to use the BICLA composite endpoint (14).

4.5 EMBLEM open label extension (SL0008) (48)

Patients who completed the 12 weeks of the EMBLEM study or who discontinued due to lack of efficacy but completed ≥ 8 weeks of the trial where eligibly for enrolment into SL0008, the open label extension to EMBLEM. Patients received 12 week treatment cycles of epratuzumab 1200mg infusions at weeks 0 and 2 (2400mg cd) plus SOC. The primary endpoint was safety of long term epratuzumab therapy.

Secondary outcomes included efficacy as defined by BILAG, SLEDAI-2k and PGA response as well as effect on HRQOL. Corticosteroid dosing during the study was analysed as well.

In total 203 patients were entered into the study with 113 completing the study. 90 (44.3%) patients discontinued the study with the most common reasons being AEs (14.3%) and lack of efficacy (11.3%). The study ran for 108 weeks in total.

AEs were reported in 192 patients (94.6%) of which 51 (25.1%) had SAEs. The most common AE was infection (68.0%), mostly urinary tract and upper respiratory tract infections. The most frequent SAEs were; severe infections (6.9%) such as sepsis or gastroenteritis, SLE flare (3.4%) and lupus nephritis (2.0%). One patient died due to pericarditis and heart failure, unrelated to the drug 43 days after the first infusion.

The percentage of patients with overall BILAG improvement without worsening compared to EMBLEM baseline increased from 34.5% at SL0008 entry to 63.8% at week 108. The proportion of responding patients was greatest in the patients previously given placebo in EMBLEM. Median BILAG and SLEDAI scores decreased at week 108 compared to the EMBLEM baseline. Mean PGA and PtGA score improved. In terms of HRQOL outcomes clinically meaningful improvements in SF-36 scores were seen at week 48 and were maintained or improved further at week 108. Corticosteroid sparing effects were observed with the median corticosteroid dosage reducing from 10.0mg/day (EMBLEM baseline and SL0008 entry) to 5.0mg/day at week 108. One confounder in this study was the relatively high number of discontinuations due to lack of efficacy. This may have positively shewed the results contributing to BILAG response and corticosteroid reductions in this study.

4.6 Japanese Phase I/II study (49)

A Japanese phase I/II multicentre, double blinded, randomised controlled trial assessed the safety, pharmacodynamics and pharmacokinetics of epratuzumab in Japanese patients with moderate to severe SLE. The treatment groups were the same as the EMBLEM study but without the 1800mg EOW group. All patients in the placebo group and 13 of the 16 epratuzumab patients reported AEs, with 2

epratuzumab patient reporting SAEs but no significant safety concerns. The drug half life was found to be 13 days and the drug concentrations increased between the first and last infusions. Immunological analysis demonstrated CD22 downregulation with a mild to moderate reduction in B cell number.

4.7 EMBODY 1 and EMBODY 2 (33)

EMBODY 1 and EMBODY 2 were two phase III multicentre, multinational, randomised double blind placebo-controlled trials looking at epratuzumab in moderate to severe SLE. It aimed to address the efficacy and safety of repeat courses of epratuzumab using 2 different regimens every 12 weeks compared to placebo (46,47). Inclusion and exclusion criteria were similar to the EMBLEM study and are summarised in table 3 and the results in table 4.

Patients were randomised to courses of placebo, epratuzumab 600mg weekly (2400mg cd) and epratuzumab 1200mg EOW (2400mg cd) in a 1:1:1 ratio. All infusions were given over a 4 week period at the start of each 12 week treatment cycle. A total of 4 cycles over 48 weeks were planned with assessments at weeks 0, 4, 8, and 12 of each cycle. The protocol allowed corticosteroids to be increased up to 25% from baseline without making the patient a non-responder up to week 8, corticosteroid reduction was encouraged but not mandated thereafter. Other immunosuppressant or anti-malarial medications had to be kept at baseline dose unless toxicity was suspected.

The primary outcome was the responder rate at week 48 according to the composite BICLA endpoint. Secondary outcomes were BICLA response at weeks 12, 24 and 36 as well as corticosteroid dose changes from baseline at weeks 24 and 48. HRQOF outcomes in the form of SF-36 and other patient reported outcomes were also measured.

In total EMBODY 1 and EMBODY 2 randomised 793 and 791 patients respectively. Baseline demographics and disease activity between groups and studies were comparable. Unfortunately 265 (33.4%) and 258 (32.6%) patients prematurely discontinued EMBODY 1 and EMBODY 2 respectively. The most common cause for

premature discontinuation was lack of efficacy in all groups. One study site in EMBODY 1 was excluded due to protocol violations, these discontinuations were spread evenly across all treatment arms.

Both studies failed to show a significant difference in the primary outcome. The BICLA response rates in EMBODY 1 were 34.1% in the placebo group, 39.8% in the 1200mg EOW group and 37.5% in the 600mg weekly group. BICLA response rates in EMBODY 2 were 33.5% in the placebo group, 34.1% in the 1200mg EOW group and 35.2% in the 600mg weekly group. Both studies observed improvements in disease activity in both placebo and treatment groups within 12 weeks of starting therapy. Both studies showed a similar number of non-responders (due to no treatment response or disallowed changes in concomitant medications) in each treatment group. About one third of patients in total discontinued the study early before week 48. This was possibly due to a perceived lack of efficacy early and the desire to enter the open label extension for which patients were eligible to enter after week 16.

The EMBODY studies also failed to show any significant difference in any of the planned secondary outcome measures. At weeks 24 and 48 a similar but relatively small proportion of patients from each treatment group had achieved reduction in corticosteroid dose (37.7-38.6% and 35.6-36.7% in EMBODY 1 and EMBODY 2 respectively). There was no significant difference in BICLA responders at weeks 12, 24 and 36. Overall there were similar improvements observed in overall BILAG-2004, SLEDAI-2K, PGA, PtGA scores and HRQOL outcomes such as SF-36 and LupusQoL in all treatment groups. Additional analyses addressing geographic region, ethnicity, baseline medications and immunological parameters showed no significant differences. Post hoc analysis using an adjusted BICLA definition of response in which rules for disallowing changes in concomitant medications were disregarded also failed to show any significant differences.

Immunological responses were comparable to the EMBLEM and ALLEVIATE studies with a medium reduction in peripheral B cells of 30-40% in patients who received epratuzumab confirming that the drug was biologically active. Epratuzumab had no

effect on T cell, IgA and IgG levels, although a 20% decrease in IgM levels was observed.

There were no new safety concerns. The incidence of adverse events was similar between all treatment groups. AEs occurred in 79.9-88.0% of all patients, the most common being infections (urinary tract and upper respiratory tract infections), headaches and nausea. SAEs occurred in 17.0-18.9% of patients, the most common being worsening of SLE. There were 5 and 4 deaths in EMBODY 1 and EMBODY 2 respectively with 4 occurring in the placebo group and 5 occurring in patients receiving epratuzumab, consistent with previous 12 month lupus trials involving patients with moderate and severe disease activity at baseline. The causes of death ranged from pneumonia and septic shock to lupus myocarditis and pulmonary embolism.

In summary EMBODY 1 and EMBODY 2 both failed to show differences in primary, secondary and exploratory outcomes. They also both showed a high placebo response rate, higher than had been seen in previous trials.

5. Conclusion

There have been a total of 7 clinical trials looking into the efficacy and safety of epratuzumab in SLE and 3 open label extension studies. Overall these trials demonstrate that epratuzumab is a well tolerated drug with similar AEs rates being reported in placebo and treatment groups. The most common AEs were simple infections such as urinary tract and upper respiratory tract infections as well as headaches, as reported in the normal population.

All trials showed effects on B cells with peripheral B cell reductions of 30-50%. Complement levels and auto-antibody levels remain unchanged. Immunoglobulin levels tended to remain constant but the EMBODY trial reported a 20% reduction in IgM levels, although this was not associated with an increased risk of infection.

Early trials, although not meeting their primary outcomes, showed promising outcomes with certain regimens and some potential corticosteroid sparing effects.

The EMBLEM trial showed a statistically significant increase in BICLA responders in the 2400mg cd (1200mg EOW or 600mg weekly) groups compared to placebo in a study with a low placebo response rate originally attributed to the use of this end-point (47). The ALLEVIATE post hoc adjusted analysis demonstrated reasonable corticosteroid sparing effects of epratuzumab, with both OLE studies (SL0006 and SL0008) also showing corticosteroid sparing effects although the impact of non-responders withdrawing may have biased the results (45,46,48). These promising results were not seen in the two EMBODY phase III RCTs, which showed no significant treatment effect of epratuzumab compared to placebo and no steroid sparing effects (33). This was a very disappointing result and it was not clear why the placebo response rate was higher than expected. It is possible that patients in trials take their regular medications (standard care immunosuppressants and anti-malarials) for lupus more consistently than the before the trial as they have regular meetings with a dedicated clinical team. This could impact on the results by increasing the proportion in all groups that responded to conventional therapy, making it harder to discriminate the benefit of additional therapy with epratuzumab particularly in the context of corticosteroids that could be increased early in the trial and without the need to follow a strict protocol for steroid reduction.

6. Expert commentary

Epratuzumab has been a promising treatment option for lupus based on its effects on B cells and the attraction of modulating B cell function to reduce auto-immune disease without causing long term significant B cell depletion that might increase the risk of infection. Unfortunately none of the studies have shown very significant benefits and most importantly the two 48 week phase 3 EMBODY trials failed to meet planned primary and secondary end-points including reduction in disease activity, improvement in quality of life and corticosteroid sparing properties. The phase 2 trials and their open label extension studies had suggested that epratuzumab had the potential to achieve such end-points.

Common to all of the controlled studies is the high placebo response rate which ranged from 21- 34.1%, and was highest in the 12 month EMBODY studies. The

reason for this high placebo response rate could be due to the intense amount of monitoring and regular interactions with expert lupus teams with far more study visits than an average patient would expect to attend clinic “in the real world”. As a result there may be more opportunity to optimise standard care, for example sunblock use and medication compliance, and hence explain the high placebo response rates. Patients continued corticosteroids and doses were increased at the start of the trials, potentially masking benefit from epratuzumab.

None of the studies measured drug levels for conventional therapy such as hydroxychloroquine or mycophenolate but there have been reports of sub-optimal levels that increased during previous studies (4). This may be particularly relevant considering that some trial centres were in countries with insurance based health care systems and varying availability of specialists to some patients with lupus, such as USA and India. Therefore some of the patients entered into the trials will have got significantly more health care input, disease monitoring and regular prescriptions than before the trials, potentially increasing response to conventional medications, hence driving up the placebo response rates and response rates in all groups unrelated to trial medication. Therefore, even if epratuzumab has a mild to moderate disease ameliorating effect the high placebo response rates would have drowned this signal out. This phenomenon of intensive outpatient management with SOC causing improved outcomes has also been described in rheumatoid arthritis (50) and discussed in another review (51). The APRIL-SLE randomised controlled trial investigating the efficacy and safety of atacicept, a B-lymphocyte stimulator (BLyS) and A proliferation-inducing ligands (APRIL) antagonist, overcame this potential confounder by first giving all patients a standard regime of corticosteroids, then only randomising patients with inactive disease in response to steroids and standard of care (52). Hence ensuring that all patients had optimised standard of care before randomisation and accessing more effectively the ability for atacicept to prevent flares. This could be applied to future SLE trials to overcome these inconsistencies, but has the drawback of not testing the drugs ability to treat flares or its corticosteroid sparing effects.

Against this hypothesis were the high rates of early discontinuation due to inefficacy, but the opportunity to move to an open label trial may have encouraged patients to withdraw early (from week 16 onwards) in the EMBODY trials to secure epratuzumab. The rates of withdrawal in the open label studies were less clearly due to lack of or loss of efficacy than in EMBODY but nevertheless the numbers were significant (44% in EMBLEM extension SL0008; 14% related to efficacy). Some patients may have had disease activity and QoL assessments confounded by chronic damage and co-morbidities such as fibromyalgia which can be confused with active lupus disease except by the most experienced physicians caring for lupus patients. Although some training was provided, not all trial centres involved physicians with specialist lupus clinics and experience of disease assessment methodology. In retrospect it is hard to assess whether the main reasons for withdrawal in the open label studies were lack of efficacy for lupus, poor perceived health due to co-morbid conditions or withdrawal of consent to continue as improved or wanting to plan pregnancy.

More patients might have continued with epratuzumab long term if the benefits from the regimen administered led to more consistent improvement in lupus facilitating more significant reductions in corticosteroids. There is a concern that the dosing regimen of epratuzumab was sub-optimal. The original dosing came from experience of epratuzumab in the treatment of lymphoma. The dosing regimen of 12 weekly cycles with 2 – 4 infusions between weeks 0 and 4 was arbitrary. Initial drug level measurements showed that epratuzumab was detectable at 4 weeks post last infusion (43). Given that the more recent assessment in the Japanese open label study (49) suggested that the half life of epratuzumab was 13 days and not 23 days as suggested in the original lymphoma studies (26, 42), perhaps the 12 weekly regimen was not optimal. The regimens used may have been sub-therapeutic for lupus although associated with some evidence of B cell modulation. In all the clinical trials the primary outcome time point was at the end of a 12 week cycle (ALLEVIATE 1, 2 and EMBLEM at 12 weeks, EMBODY 1 and 2 at 48 weeks). There have been anecdotal, unsolicited and uncontrolled reports from patients in the open label studies that they derived benefit from the drug but that the effects only lasted 6-8 weeks after each infusion course. Therefore by the time of assessment the drug levels may not have been optimal resulting in inability to document significant

improvement. Most monoclonal antibodies given by IV infusion are administered on a 4-8 weekly basis. The possibility of administering epratuzumab more frequently to maintain higher drug levels has not been tested in lupus. The reduction in B cell numbers has been taken as evidence of biological efficacy but few studies addressing its other mechanisms of action on autoimmune disease (eg cytokines, cell migration etc) have been undertaken. Only very limited regimens were tested in the phase 2 studies, and additional studies looking at different regimens using different dosing and retreatment schedules might have been more successful than using the 12 week cycle regimen.

Another disadvantage of these studies is that they have excluded patients with severe renal and neuropsychiatric disease as well as patients with anti-phospholipid syndrome that might have benefitted most from B cell modulation as they are less likely to respond promptly to conventional therapy with azathioprine, methotrexate, mycophenolate mofetil and anti-malarials (usually hydroxychloroquine). Such patients have derived benefit from rituximab in many open label studies of patients refractory to conventional therapy even though rituximab failed its phase 3 randomised controlled trials (4).

The possibility of other sub-groups of lupus patients responding to epratuzumab has been raised by recent post-hoc analyses of EMBODY. These have suggested that lupus patients that have anti-SSA (anti-Ro) antibodies and self-reported clinical sicca symptoms associated with Sjogren's syndrome may benefit from epratuzumab as they show the best BICLA response rates (53). The post hoc analysis identified 112 lupus patients with a diagnosis of Sjogren's syndrome who were anti-SS-A positive, of which 40 had received placebo and 72 had received epratuzumab. A statistically significant higher BICLA response rate was seen at 24 weeks in patients receiving epratuzumab compared to placebo but there was a non-significant difference at 48 weeks. Epratuzumab was well tolerated with no difference in the frequency of adverse effects between groups. It is important to emphasize that this analysis was post-hoc and aimed at hypothesis generation. It is unclear whether this is a potential subgroup that may benefit from epratuzumab or is just an artefact of post-hoc analysis, further prospective studies are needed to confirm this. There is no specific

mechanism as to why this subgroup may benefit and this is another reason why the finding should be interpreted with caution.

The reason why epratuzumab has failed to show efficacy could be because CD22 is the wrong target. Rituximab and belimumab are the B cell therapies that have shown clinical efficacy (albeit with mixed results). Rituximab targets CD20, which is selectively expressed by pre-B and mature B cells. The main mechanism of action is through depletion of these subgroups secondary to ADCC and CDC. Belimumab on the other hand targets soluble B-lymphocyte stimulator (BLyS), a cytokine that is vital in B cell development, proliferation and survival (51). Both rituximab and belimumab result in substantial depletion of circulating B cells and normalisation of complement, unlike epratuzumab which works via immunomodulation and is associated with less B cell depletion. The results of the epratuzumab, rituximab and belimumab studies are reasonably comparable as the study designs were all very similar. The EXPLORER (rituximab) study (54), used classic BILAG as the outcome and the BLISS-52 and BLISS-76 (belimumab trials 19,20) used the SLE responder index (similar to the BICLA index – see table 2). One of the reasons why the rituximab studies failed to demonstrate efficacy was because for a patient to be a responder they were not allowed any new BILAG B grade disease. This meant that patients could improve in all systems but then develop a photosensitive rash due to failure to wear sun protection making them a non-responder, even if the rash was less severe than at baseline. For this reason the definition of a BILAG responder was changed in the belimumab and epratuzumab studies to allow 1 new BILAG B score and this is the major difference between the studies. The rituximab trials also used a lot of corticosteroids early in all patients, much more than most other studies, which may have reduced the ability to detect difference in outcomes between groups with relatively small numbers of patients compared with the belimumab trials (19,20).

Further work is looking at combining biological therapies in SLE. A current trial is investigating the combination of rituximab followed by belimumab in the treatment of lupus. This is based on the observation that after rituximab mediated depletion of B cells there is a peak in soluble BLyS (55). Epratuzumab has been used in combination with rituximab in the treatment of non-Hodgkin’s lymphoma showing

both efficacy and safety (56). Epratuzumab might have a role in combined biological therapy for SLE as well.

The other possibility is that B cells are the wrong target. Type 1 interferons and the co-stimulation pathways; inducible T-cell co-stimulator (ICOS), CD40 and TNF-like weak inducer of apoptosis (TWEAK) are all promising potential targets some of which are subject to ongoing clinical trials (51).

7. Five year view

The likelihood of there being another clinical trial for epratuzumab in SLE soon is unlikely with UCB terminating its collaboration with Immunomedics for the development of epratuzumab for autoimmune disease (57). However a recent post hoc analysis of the EMBODY trials has demonstrated possible efficacy of epratuzumab in anti-SSA positive patients with lupus and features of Sjögren's Syndrome (53). An earlier open label phase I/II study looking at epratuzumab in primary Sjögren's syndrome demonstrated some efficacy and drug safety (58). The primary endpoint in this study was a composite endpoint of Schirmer's test, fatigue, whole salivary flow and erythrocyte sedimentation rate (ESR). This could potentially open the door for further trials investigating the role of epratuzumab in the management of Sjogren's syndrome and the subgroup of patients with SLE and Sjogren's syndrome in whom B cell modulation by epratuzumab may be most effective. There is also ongoing clinical research looking into the use of epratuzumab in follicular lymphoma and acute lymphoblastic leukaemia, however this is beyond the scope of this review.

Key Issues

- The pathogenesis of SLE is primarily thought to be B cell mediated
- Disease activity in SLE is measured using the disease activity indices BILAG-2004 and SLEDAI-2K and the composite end-point BICLA includes these, PGA and no need for additional immunosuppressive treatment
- Epratuzumab is a humanized CD22 targeted IgG1 monoclonal antibody

- Epratuzumab works by activation of CD22 with causes immunomodulation of B cells via changes in surface receptor expression, cytokine expression, reduction in plasma cell generation and effects on cell adhesion and migration
- It has B cell specificity, reducing peripheral B cell count by 30-50% without having major effect on immunoglobulin levels or other parts of the immune system
- Epratuzumab has good tolerability and safety profiles
- All randomised controlled trials have failed to show a significant difference in primary endpoints between epratuzumab and placebo groups using 12 week cycles of epratuzumab
- It is not clear why trials have failed to demonstrate efficacy but high placebo response rates from optimisation of standard of care and sub-optimal dosing regimen may have played a role
- Post-hoc analysis of the EMBODY phase III RCT highlighted patients with anti-SSA and Sjogren's syndrome as a possible subgroup of SLE patients who may benefit from epratuzumab, so further research is needed to explore this and other potential sub-groups that might respond.

Information resources:

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Figure 1 legend

Immunomodulatory mechanisms of epratuzumab. Epratuzumab dependent down regulation of the adhesion molecules CD62L and β7 integrin inhibiting recruitment of B cells to inflamed tissue. Epratuzumab dependent internalisation of CD22 and of CD79α resulting in reduced BCR signalling. Epratuzumab dependent down regulation of CD19, CD79β and CD21 via trogocytosis, resulting in reduced BCR signalling. Epratuzumab dependent inhibition of the pro-inflammatory cytokines TNF and IL-6 whilst preserving the anti-inflammatory cytokine IL-10.

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