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Treatment of systemic lupus erythematosus with epratuzumab

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Systemic lupus erythematosus is a prototypic autoimmune disease characterized by abnormalities in the activity of B-cells and T-cells. A novel specific treatment for autoimmune diseases is B-cell depletion with monoclonal antibodies. Epratuzumab is a monoclonal antibody that targets CD22 antigen on B-cells. Initial phase II and two terminated early phase III studies suggest that treatment of systemic lupus erythematosus with this immunomodulatory agent is effective, well tolerated and significantly improves the patient's quality of life. *In vitro* studies and clinical trials with non-Hodgkin lymphoma patients indicate epratuzumab can potentially serve as a complementary drug in combination therapy with another inhibitor of B-cell activity, rituximab, which is a monoclonal anti-CD20 antibody.

Introduction

Systemic lupus erythematosus (SLE) is a classic autoimmune disease affecting approximately half a million people in Europe and a quarter of a million in the United States of America (24–65 in 100 000 individuals), mostly women in their childbearing years [1, 2]. Its pathogenesis remains unclear. The complex interactions between genetic (multiple susceptibility genes), hormonal (possible involvement of abnormal oestrogen metabolism, defective hypothalamo-pituitary-adrenal axis), immunologic and environmental factors are probably required to trigger the disease [3]. The currently approved treatments including non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, steroids and immunosuppressive drugs are non-specific and associated with serious adverse events. Moreover, a significant number of patients show only partial or no response to the approved therapies [4]. Therefore, more specific treatments have been intensively sought in recent years. Because B-cells are considered to play a central role in the pathogenesis of SLE, they represent targets of new therapies, which include B-cell depletion using monoclonal antibodies against B-cell surface antigens or B-cell survival factors. Established therapeutic approaches are anti-CD20 monoclonal antibodies, anti-CD22 antibodies, anti B-cell activating factor (Blys/BAFF) antibodies, monoclonal antibodies or fusion proteins against co-stimulatory molecules involved in B-cell/T-cell interaction and B-cell tolerogens [5] (see Table 1). Although the use of epratuzumab (anti CD22 monoclonal antibody), shown to be therapeutically active in non-Hodgkin lymphoma (NHL) and primary Sjogren's syndrome (pSS), is far less advanced than rituximab (anti CD20 antibody) [6], the available data from phase II and III studies suggest it is an effective and relatively safe drug as far as managing moderate and severe SLE is concerned.

Role of B-cells in SLE

Pathogenesis of SLE is characterized by a myriad of immune system aberrations that involve B-cells, T-cells and cells of monocytic lineage resulting in polyclonal B-cell activation, autoantibody production, hypergammaglobulinaemia, immune complex deposition and, eventually, end-organ damage. The central immunological phenomenon is production of autoantibodies, which are directed at several cell molecules in the nucleus, cytoplasm and cell surface, in addition to soluble molecules such as IgG and coagulation factors. Antinuclear antibodies (ANA), present in more than 95% of patients, are most characteristic [5]. In particular, anti double-stranded DNA (anti ds DNA) antibodies, unique to SLE patients, have been associated with renal flares of the disease. Loss of B-cell tolerance, the likely cause of accumulation of large numbers of autoreactive B-cells, is probably an early and defining event in the pathogenic process [7, 8].

B-cells develop from haematopoietic stem cells (HSCs) to early-stage B-cells (pro-B and pre-B) in the bone marrow. The cells move out to the peripheral lymphoid organs and

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Table 1

Biologic agents targeting B-cells for the treatment of SLE

Agent	Structure	Target	Target characteristics	References
Rituximab	Chimeric mAb	CD20	Membrane protein, low internalization rate	[45, 48]
Ocrelizumab	Humanized mAb	CD20	As above	[55]
Epratuzumab	Humanized mAb	CD22	Membrane protein, rapid internalization rate	[34]
Belimumab	Human mAb	BAFF	B-cell survival factors	[56]
Atacicept	Fusion protein	BAFF and APRIL	B-cell survival factors	[57]
Abatacept	Fusion protein	CD28, CTLA4 receptors, B7	Cell-surface costimulatory ligands	[58]
BG 9588	Humanized mAb	CD40L	Costimulatory molecule	[59]
IDEC 131	Humanized mAb	CD40L	As above	[60]
Abetimus (LJP394)	Synthetic tolerogen molecule	BCR	Cell-surface ligand, positive or negative signal, depending on context	[61]

mAb, monoclonal antibody; BAFF, B-cell activating factor; APRIL, a proliferation-inducing ligand; CTLA4, cytotoxic T-lymphocyte antigen.

differentiate immature B-cells to transitional B-cells and then to activated mature B-cells, and in the end to memory B-cells or plasma cells B-cells (short- and long-lived), which produce immunoglobulins (some of them are autoantibodies) [9].

Although active SLE is often associated with B-cell lymphopaenia (naive and memory B-cells CD20+ CD38- are about 90% reduced [10]), certain B-cell subsets (autoantibody-secreting B-cells, oligoclonal plasma cell precursors and pregerminal centre cells) are expanded in the peripheral blood [10–12]. B-cells in SLE patients are more sensitive to the stimulatory effects of cytokines such as interleukin (IL)-6 than non-SLE B-cells. The development of SLE is preceded by these B-cell abnormalities, as well as by a positive antinuclear antibody (ANA), often by many years [9].

B-cells most probably have various functions in the development and maintenance of SLE [13, 14]. They were first suspected to participate actively in SLE pathogenesis because plasma cells produce autoantibodies [9]. However, the direct role of SLE autoantibodies in pathology has been hard to establish, as there are numerous examples in literature highliting the importance of antibody-independent abnormalities [15–17]. Results of these studies raise the possibility that therapies targeting B-cells but not affecting plasma cells, immunoglobulins or autoantibodies might be effective in SLE [18]. Modulation of autoimmune responses by B-cells via antigen-independent functions may be achieved with antigen-specific B-cells, which act as antigen presenting cells (APCs) for antigen-specific T-cells in SLE models [14]. B-cells also participate in organizing and regulating inflammatory responses through cytokine and chemokine secretion. Moreover, B-cells induce lymphoid neogenesis through surface-bound lymphotoxin, which recruits and activates follicular dendritic cells, thus generating lymphoid follicles. The influence on myeloid dendritic cells and regulatory T cells was reported as well [18].

In B-cells obtained from SLE patients, several intrinsic defects, like increased expression of CD154, CD80, CD86 and IL- 10 [19–21] were detected. Other studies showed substantially enhanced mutational activity of *Vk* gene compared with normals [22]. The increased mutational activity may play a role in the development of autoreactivity in SLE patients. In addition, B-cell receptor (BCR) signaling defects have been observed in SLE patients. They result in upregulation of calcium mobilization and tyrosine phosphorylation upon activation of BCR [6]. Another unique feature of lupus-associated B-cells, specifically those targeting nucleic acid containing autoantigens, is their activation through the synergistic engagement of BCRs and toll-like receptors (TLRs) [23].

Therefore, the special interest in monoclonal antibodies that target B-cells directly and bind to B-cell surface antigens, such as CD20 or CD22, is clearly well-founded.

CD22 molecule

CD22, the second candidate antibody target for SLE therapy after CD20, is a 135 kDa B-cell-specific transmembrane sialoglycoprotein. It is expressed at low levels in the cytoplasm of pre-B-cells and its localization shifts to the cell surface and higher levels on mature IgM + IgD + B cells [11]. CD22 is absent on plasma cells and memory B cells [9].

CD 22 has been shown to play role in the regulation of B-cell function, both as lectin-like adhesion receptor and as a component of the B-cell activation complex. The function of CD22 through the BCR complex is due to phosphorylation of three tyrosine-based inhibitory motifs (ITIM) on its intracellular tail upon BCR stimulation. Phosphorylation of CD22 leads to recruitment of tyrosine phosphatase 1 (SHP-1) and other effector molecules which in turn limit BCR signalling [24, 25]. Studies in CD22 deficient mice and CD22-negative cell lines indicated CD22 acts as a negative regulatory molecule limiting the intensity of BCR-generated signals through the mechanism of controlling calcium efflux in B-cells [26, 27]. The study on a murine model showed CD22 deficiency induced reduction of

mature B-cell numbers in the bone marrow and circulation, a shorter life span and enhanced apoptosis of B cells [28].

Murine and human studies link CD22 polymorphisms to SLE [29]. In mice with disrupted CD22 gene, hyperresponsiveness of B cells to BCR crosslinking and, paradoxically, a deficit in response to T-cell independent antigens, were observed. The lack of CD22, in conjunction with other genetic risk factors, heightens the probability of developing SLE [28, 30]. In addition, mouse strains that spontaneously develop SLE on a multigenic basis preferentially express CD22 with functional deficiencies [31]. In the human study, there was a mariginally higher prevalence of one of the genetic variations in SLE patients than in healthy individuals [32].

Its restrictive expression, in particular, makes CD22 an interesting target for therapy. However, CD22, like CD19, is rapidly internalized by B-cells. Therefore it is relatively poor target for unconjugated antibodies designed to kill through binding to cell surface. Unconjugated CD-22 specific antibodies tend to have low cytolytic activity [33], but epratuzumab has been shown to induce moderate B-cell depletion [34, 35].

Structure, pharmocokinetics and pharmacodynamics of epratuzumab

Epratuzumab is a humanized anti-CD22 IgG1 monoclonal antibody. It contains a murine sequence comprising 5–10% of the molecule, the remainder being human framework sequences, which greatly reduces potential for immunogenicity [6, 12].

Epratuzumab binds to the CD22 third extracellular domain (epitope B), without blocking the ligand binding site, with measured affinity of $K_d = 0.7$ nM. *In vitro* studies showed epratuzumab induces CD22 phosphorylation by binding to its surface [12]. It results in modulation, mostly negative, of BCR activation. This involvement of CD22 with BCR may be operative in epratuzumab's activity against NHL and certain autoimmune diseases, like pSS or SLE [11, 36]. Modulation of second key CD22 function, i.e. B-cell homing, is realized through rapid internalization on ligation with epratuzumab [9]. The CD22 surface expression is being decreased by epratuzumab, as observed both *in vitro* and in clinical studies [37].

Treatment with epratuzumab leads to a marked decrease of peripheral B-cells count (by about 35–40%) in SLE patients [34], mainly CD27-subset, suggesting that these cells, which generally comprise naive and transitional B-cells, are preferentially targeted *in vivo* [37]. Epratuzumab induces moderate, but significant antibody dependent cellular cytotoxicity (ADCC), without showing direct apoptotic or complement-mediated killing [12]. ADCC may be in part responsible for B-cell depletion seen *in vivo* with epratuzumab [35]. This monoclonal antibody mediates no complement-dependent cytotoxicity (CDC). Part of the reason may be the distance between the epitope to which epratuzumab binds and the plasma membrane, precluding the activation of the complement cascade. Another possible explanation for the lack of CDC as well as the modest ADCC activity of epratuzumab is its rapid internalization following antigen binding, resulting in reduced cell surface expression of CD22 [12, 36].

Therapy with epratuzumab does not lead to consistent decreases of ANA and anti-ds DNA antibodies, as was shown in the initial clinical trial. Post-treatment evaluations indicate it also does not affect C3 complement component levels in SLE patients [34].

Of interest, *in vitro* analysis using material collected from 12 SLE patients showed additional regulatory effects of the drug by reducing the enhanced activation and proliferation of anti-immunoglobulin-stimulated lupus B-cells after co-incubation with CD40L or CpG. Epratuzumab was observed to have inhibited the proliferation of B-cells from patients with SLE but not normal patients under all culture conditions [37].

Currently available pharmacokinetic results come from phase I/II studies including patients with chemotherapy-refractory NHL, SLE and pSS. Pharmacokinetic analyses showed that mean maximum antibody levels generally increased with increasing epratuzumab dose. In NHL studies the mean serum half-life ($t_{1/2}$) increased from 6.9 days to 26.5 days between the first and the fourth infusion [38, 39], while the highest serum values (C_{max}) increased with subsequent doses. Those characteristics are likely due to the saturation of CD22 binding sites [11]. In the study with SLE patients epratuzumab serum concentrations were measurable at 10 weeks post-infusion (in all samples) and were still detectable at 18 weeks (in five of seven samples) [34]. Noncompartmental pharmacokinetic analysis indicated a serum $t_{1/2}$ after the fourth infusion comparable with the $t_{1/2}$ of human IgG_1 (21 days), of 23 days in NHL patients [38, 39] and 15 ± 8 days in pSS patients [40].

Efficacy and quality of life in systemic lupus erythematosus

Epratuzumab efficacy in SLE was evaluated in one phase II study and two terminated early phase III studies (see Table 2).

The initial phase II open-label, non-randomized single centre study [34] was conducted in order to obtain preliminary evidence of therapeutic activity of epratuzumab in SLE, to confirm the safety, tolerance and lack of its immunogenicity in this population and to evaluate pharmacodynamic parameters. A total of 14 Caucasian patients (13 females and 1 male; 23 to 53 years old) were enrolled. Participants were required to be diagnosed with SLE ($\geq$4 American College of Rheumatology revised criteria), with the disease lasting a minimum 6 months (median was 10

Table 2
Clinical studies of epratuzumab in SLE

Study	Study design	Duration	Effectiveness	Safety
Initial clinical trial [34]	Phase II open-label, non-randomized single centre study; $n = 14$; 4×360 mg m^{-2} every other week with analgetic/antihistamine premedication; low-dose corticosteroids permitted during study	32 weeks	B-cell depletion (median of 35% at 18 weeks) in 11/11 pts within 6–32 weeks; Total BILAG score decreased by ≥50% in 14/14 patients at some point within 6–32 weeks	Well tolerated; five infections, six mild transient infusional reactions
SL0003 and SL0004 [35, 41–43]	Phase III randomized placebo controlled multicentre studies; $n = 90$; 360 mg m^{-2} ($n = 42$) or 720 mg m^{-2} ($n = 11$) at weeks 0,1,2 and 3; subsequently two infusions 1 week apart every 12 weeks; up to four treatment cycles; placebo ($n = 37$); antimalarials/immunosuppresives unchanged; corticosteroids increased at baseline, tapering initiated at week 4	48 weeks	B-cell depletion: 35% (360 mg m^{-2}), 71,5% (720 mg m^{-2}), 19% (placebo) at week 24; significantly greater reductions of total BILAG scores *vs.* placebo at 4–48 weeks	Well tolerated; nine *vs.* eight (placebo) serious infections; nine *vs.* seven mild infusion reactions
NCT00383513 [44]	Phase III open-label multicentre re-treatment trial for patients previously randomized into SL0003 and SL0004 trials; $n = 30$ (estimated); 360 mg m^{-2}; two consecutive weekly administrations followed by 12 week maintenance cycles	4 years (time frame for primary and secondary outcome measures)	Not published (estimated study completion date: 2014)	Not published

BILAG, British Isles Lupus Assessment Group.

years), at least one elevated autoantibody level, moderately active SLE (a score of 6 to 12 for British Isles Assessment Group disease activity (BILAG, median was 10) and be naive to antibody drugs at study entry. Patients were receiving corticosteroids ($n = 13$, 1–12 mg day^{-1} prednisolone) plus immunosuppressives ($n = 11$, including 50–200 mg day^{-1} azathioprine, $n = 9$; 20 mg week^{-1} methotrexate, $n = 2$; 2 g day^{-1} mycophenalate mofetil, $n = 1$), and antimalarials ($n = 6$, 200–600 mg day^{-1} hydroxychloroquine).

The participants received four doses of 360 mg m^{-2} epratuzumab intravenously administered every other week with paracetamol (acetaminophen) and antihistamine given as premedication prior to each use to decrease the risk of immune reactions to epratuzumab. The effectiveness of epratuzumab was evaluated at 6, 10, 18 and 32 weeks using numerical BILAG scores as well as categorical scores. The compositions of B- and C-level activities improved after therapy, primarily in the general, mucocutaneous and musculoskeletal systems. There were also marked changes in renal and neurological domains of C-level activities. Statistically significant improvement in the total BILAG score was observed at 6, 10 and 18 weeks with a substantial proportion of patients showing 50% or more improvement (77%, 71% and 38% at weeks 6, 10 and 18, respectively). At the final 32 week evaluation, there was also statistically significant improvement in total BILAG score (15% of patients achieved 50% or more improvement). However, achieving 50% or more improvement in the total BILAG score, from 77% at week 6 to 15% at week 32 suggests a short duration of effect. In many patients B- and C-level activities resolved persistently, but the heterogenicity of patients' manifestations and the limited number of study participants precluded the identification of a preferential response profile to the drug. Worsening of BILAG categorical scores compared with baseline was infrequent. Only two patients (14%) showed deterioration of hematological parameters, one starting at 6 and the other at 18 weeks. Renal (mild proteinuria) deterioration was manifested by another patient at 10 weeks.

SL0003 and SL0004 were randomized controlled phase III trials prematurely discontinued due to interruptions in medication supply. The studies were similar in design. They included SLE patients with severe (BILAG A; SL0003) and/or moderate (BILAG B in at least two body systems/organs; SL0004). Analyses were combined to increase available data. The results were presented in 2008 and are available only as congress abstracts [35, 41–43].

Ninrty patients were randomized to receive placebo ($n = 37$), epratuzumab 360 ($n = 42$) or 720 mg m^{-2} i.v ($n = 11$). First treatment cycle infusions, of four in a 48 week study, were to occur at weeks 0, 1, 2 and 3. They were to be followed by cycles of two infusions 1 week apart, every 12 weeks. Corticosteroids were increased at baseline (tapering was initiated at week 4); immunosuppresives and/or antimalarials continued unchanged. Primary endpoint was reduction of all BILAG A to B, BILAG B to C, no worsening in other systems and no addition or increase in immunosuppresives/antimalarials or corticostroids above tapering levels (by weeks 20–24 patients were to reduce corticosteroids to ≤10 mg prednisone equivalents once daily in SL0003 or ≤7.5 mg once daily in SL0004). Treat-

ment with epratuzumab at both doses resulted in better reductions in total BILAG scores than placebo from study weeks 4 through 48. At week 12 the mean reductions in epratuzumab 360, 720 mg m^{-2} and placebo groups were 6.4, 7.2 and 5.8, respectively. At 48 weeks the reductions were 6.9, 9.0 and 5.4, respectively. Efficacy was most consistent in the largest group receiving epratuzumab 360 mg m^{-2} [41].

SL0003 and SL0004 studies showed that epratuzumab treatment enables clinically meaningful steroid sparing compared with placebo. At weeks 20–24, 75% (24 of 32) of patients receiving the lower and 100% (6 of 6) the higher dose of epratuzumab achieved corticosteroid tapering criteria compared with 56.5% (13 of 23) receiving placebo. Using an ANOVA model adjusting for race and medication at baseline, it was shown epratuzumab treated patients used less corticosteroids than placebo patients over 24 weeks [42].

Epratuzumab treatment at both doses significantly improved patients' quality of life. Physician's (MDGA) and patients' global assessment (PGA) as well as the Short-Form 36 Health Survey (SF-36) were evaluated at baseline and every 4 weeks. Improvements in the placebo group occurred early and lessened over 24–48 weeks. In contrast, more evident, large improvements were observed over 12–48 weeks with epratuzumab 720 mg m^{-2} and 36–48 weeks with epratuzumab 360 mg m^{-2}. At 48 weeks mean changes from baseline in the epratuzumab 360 and 720 mg m^{-2} groups exceeded placebo in SF-36 mental (4.7, 10.2, 3.4, respectively) and physical component summary scores (7.5, 6.3, 2.4) as well as in PGA (0.9, 1.4, 0.4) and MDGA scores (0.9, 1.4, 0.4). The changes correlated with sustained improvements in BILAG [43].

Another phase III study (NCT00383513) with patients previously randomized into the SL0003 and SL0004 studies is currently on-going with an estimated completion date of February 2014. The study is aimed at obtaining long-term information concerning efficacy and safety of epratuzumab treatment [44].

Safety

Epratuzumab has been generally well tolerated among the SLE patients in phase II and phase III studies.

During the initial open-label trial a total of 10 patients (of 14 patients enrolled) reported adverse events. Most of them ($n = 6$, 43%) were transient mild-to-moderate (grade 1–2) infusional reactions and one patient experienced somnolence following antihistamine medication. Five patients (36%) developed infections (including herpes zoster, otitis media, *Helicobacter pylori*-associated gastritis, vaginitis/vaginal candidiasis, cystitis and tonsillitis). Serum samples for analysis of pharmacokinetics and immunogenicity (HAHA, human anti-human antibody) by ELISA assay were collected in a limited number of patients post-treatment at 6 ($n = 12$), 10 ($n = 7$) and 18 weeks ($n = 7$). No evidence of immunogenicity was detected in the initial trial [34].

In the phase III trials the occurence of adverse events was similar between epratuzumab and placebo groups. There were seven (18% of patients) infusion adverse events (grade 1 or 2 and mostly during first three infusions) in patients treated with epratuzumab 360 mg m^{-2}, two (18%) with epratuzumab 720 mg m^{-2} and seven (19%) with placebo. Serious infections occurred in five (12%), four (36%) and eight (22%) cases, respectively. In three (27%) patients from epratuzumab 720 mg m^{-2} and three (8%) patients from placebo groups adverse events led to withdrawal. A low incidence of immunogenicity (HAHA) was observed [42].

These observations are consistent with the data obtained from clinical trials with over 400 NHL patients or other B-cell malignancies [34] and an open-label trial conducted in 15 patients with pSS, with most treatment-related events being mild-to-moderate infusion reactions, occurring mainly during the first infusion [40].

In all epratuzumab studies patients were screened for latent tuberculosis before inclusion. No case of tuberculosis during epratuzumab therapy or follow-up was reported.

Combination therapy with rituximab

Rituximab, a chimerized anti-CD20 monoclonal antibody, was the first agent acting against B-cell surface antigen to obtain official authorization in autoimmune disease (rheumatic arthritis) and widespread clinical use [11]. A number of prospective open-label SLE studies and several retrospective cohort studies were reported. Six studies indicated rituximab was effective for the treatment of adult and children-onset SLE in about 140 patients with clinical response of >80% [9]. However, recent randomized placebo-controlled studies have not corroborated the results of the earlier smaller trials [18, 45]. It should be noted that some problems with design and outcome measures of the latest trials may have contributed to the disappointing results [18, 46].

The initial experience with epratuzumab, similarily to rituximab, was with B-cell lymphoma treatment [38, 39, 47]. The two drugs, as shown in *in vitro* studies, represent very distinct modes of action. Epratuzumab acts more as an immunomodulatory agent, in addition to its cytotoxic role, while rituximab is an acutely cytotoxic therapeutic antibody [12, 36]. Mechanisms of rituximab cytotoxicity include CDC and, induced *in vitro*, ADCC [36]. Accumulating evidence suggests rituximab can also directly induce apoptosis [6]. Contrary to rituximab, with epratuzumab no CDC or induced apoptosis could be detected. ADCC was less than rituximab, but significant [36]. Another difference is

the very low level of immunogenicity with epratuzumab [34, 42], contrasting with the experience of rituximab in SLE, where development of HACA (human anti-chimeric antibodies) was observed in up to 5% of patients [48, 49]. The B-cell depletion induced by epratuzumab, as shown in NHL [38, 39], SLE [34, 35] and pSS trials [40] was markedly less than rituximab [48, 50].

Combining rituximab and epratuzumab *in vitro* did not decrease the ability of rituximab to induce apoptosis, CDC and ADCC, suggesting it may yield additional therapeutic benefit. As stated above, epratuzumab does not induce CDC, probably responsible for a large part of the efficacy of rituximab, but also shown to correlate with the occurrence of severe first-dose effects of rituximab treatment [36].

The therapeutic advantage of combining epratuzumab with rituximab, without increased host toxicity, has been suggested in single- and multi-centre trials in NHL patients [51, 52]. Moreover, potentiation of anti-CD20 activity has been observed in *in vivo* animal studies when epratuzumab was combined with rituximab or hA20, the humanized monoclonal anti-CD20 antibody [53, 54].

Conclusion

Epratuzumab is a humanized anti-CD22 IgG monoclonal antibody, one of the new B-cell depleting agents. Considering its pharmacological features, epratuzumab is a potential therapeutic agent in SLE, alternative or supplementary to the current therapies. The results of one phase II and two terminated early phase III clinical trials suggest SLE therapy with epratuzumab is effective, generally safe and improves patient's quality of life. Frustratingly, the latter trials were prematurely discontinued, because of interruptions in medication supply, before they could have finally proved effectiveness and safety of the drug. The on-going phase III trial and other future trials may complete data required for the formal approval process. *In vitro* studies indicate epratuzumab has a distinctly different mode of action from rituximab and combination therapy of these drugs is possible and potentially beneficial. The reports emphasize the need for clinical studies assessing the combination therapy in SLE and other diseases responding to both epratuzumab and rituximab.

Competing Interests

There are no competing interests to declare.

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