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FULL REVIEW

‘That Obscure Object of Desire’: in systemic lupus erythematosus B-cell activating factor/B-lymphocyte stimulator is targeted both by the immune system and by physicians

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ABSTRACT

Systemic lupus erythematosus (SLE) is characterized by autoantibodies that mediate tissue injury. However, the pathogenesis of SLE remains poorly understood and available therapeutic approaches are not fully satisfactory. Belimumab, a monoclonal antibody that neutralizes B-cell activating factor (BAFF), was the first drug approved to treat SLE in more than 50 years. However, it is not labelled for use in severe lupus nephritis. Recently, a novel high-throughput multiplex protein microarray platform to profile circulating immunoglobulin G (IgG) autoantibodies in SLE patients identified IgG autoantibodies against several cytokines and growth factors at higher titres in SLE patients than in controls. The presence of autoantibodies to BAFF was validated in a subset of SLE patients by enzyme-linked immunosorbent assay. Low levels of anti-BAFF autoantibodies were also present in healthy controls. The association of anti-BAFF reactivity to clinical features and response to therapy was not addressed. However, preliminary data suggested an association to an interferon-α-responsive mRNA signature, itself associated with severity. Functional studies disclosed a neutralizing activity of autoantibodies against BAFF. These findings raise new questions regarding the role of BAFF in SLE and the functional and therapeutic significance of anti-BAFF and anti-cytokine autoantibodies.

Keywords: autoimmunity, b cells, lupus, TNF superfamily

INTRODUCTION

In the movie ‘That Obscure Object of Desire’ an aging Frenchman falls in love with a young Spanish woman who repeatedly frustrates his overtures [1]. This female character had only one suitor, unlike the two suitors targeting tumour necrosis factor ligand superfamily member 13b (TNFSF13B), also known as B-cell activating factor (BAFF), B-lymphocyte stimulator (BLyS) and CD257. In systemic lupus erythematosus (SLE) patients, both physicians and the patient’s own immune system may target BAFF with neutralizing antibodies. The European Medicines Agency (EMA) authorized in 2011 the use of the monoclonal antibody belimumab (Benlysta) to treat SLE [2]. The therapeutic benefit of belimumab is consistent with both

the role of BAFF as a B-cell survival and maturation factor, and with our current understanding of the pathogenesis of SLE as a disease characterized by polyclonal B-cell activation leading to the production of multiple autoantibodies. Surprisingly, BAFF is also courted by the immune system. A serum factor protein microarray detecting circulating autoantibodies identified elevated IgG reactivity to BAFF in serum from SLE patients [3]. Anti-BAFF autoantibodies correlated with features associated with the severity of SLE. How can we reconcile these apparently contradictory observations? Can anti-BAFF antibodies be both a therapy for SLE and a pathogenic mechanism or marker for disease severity?

UNSOLVED ISSUES IN SLE AND LUPUS NEPHRITIS

SLE is an autoimmune disease of unknown aetiology that results in heterogeneous clinical manifestations in multiple systems and organs. Given the protean manifestations, classification criteria were proposed by the American College of Rheumatology and were recently updated by the Systemic Lupus International Collaborating Clinics (SLICC) group [4]. The 2012 SLICC classification introduces low complement levels as a criterion and also allows classification as SLE only on the basis of biopsy-proven nephritis compatible with SLE in the presence of antinuclear or anti-dsDNA antibodies. SLE may lead to early death as a result of disease activity, infections or accelerated atherosclerosis [5]. The 10-year survival rate is about 70–90% [6]. Patients with SLE are treated with non-steroidal anti-inflammatory drugs, antimalarial agents, glucocorticoids and immunosuppressive drugs. Class III/IV lupus nephritis is the most severe nephrological presentation and may lead to end-stage renal disease [7]. Clinical guidelines recommend combining immunosuppressive drugs and steroids for severe lupus nephritis [7–9]. However, currently available immunosuppressive drugs are non-specific and may increase the risk of severe, life-threatening infection and malignancy. Cyclophosphamide may negatively impact on fertility. Furthermore, induction of remission may be delayed for months or not be achieved [7]. Thus, novel therapeutic approaches are needed, which decrease the risk associated with non-specific immunosuppression, increase the response rate of severe flares and decrease the time to a complete response and long-term sequelae. Novel concepts under study include adding a nephroprotective agent, such as neutralizing anti-tumor necrosis factor-like weak inducer of apoptosis (TWEAK) antibodies [10], on top of immunosuppressants to accelerate remission. However, the first drug approved for the treatment of SLE in more than 50 years is another immunosuppressant, belimumab. Although subgroup analysis of patients with mild-to-moderate kidney involvement enrolled in Phase III trials suggested a potential renal benefit [11], belimumab is currently not labelled for use in severe lupus nephritis or encephalopathy as these patients were excluded from trials [2]. A belimumab renal response outcomes trial is expected to be completed by 2017 [12, 13].

People of African or Hispanic ancestry tend to have a higher prevalence of SLE and more severe kidney disease than other ethnic groups [5, 14]. However, the underlying pathogenic factors and how they should impact the therapeutic approach are poorly understood. In this regard, the pathogenesis of SLE is complex. Genetic, environmental, hormonal, epigenetic and immunoregulatory factors result in immune system deregulation leading to tissue injury by autoantibodies, immune complexes, autoreactive or inflammatory T cells and inflammatory cytokines [5]. Despite this complexity, B cells are considered to be central to the manifestations of SLE.

B-CELL TARGETED THERAPIES IN SLE

In SLE, B cells secrete autoantibodies with multiple specificities that mediate tissue damage and also present autoantigens to T cells [5]. Thus, B cells have been targeted therapeutically. Anti-CD20 antibodies were the first biologicals targeting B cells. However, development of three anti-CD20 agents for SLE has been discontinued [12]. Two rituximab Phase III trials, the exploratory Phase II/III SLE evaluation of rituximab (EXPLORER) trial in active SLE and the LUNAR trial in lupus nephritis, failed to meet their primary outcomes [15, 16]. An ocrelizumab Phase III trial in active lupus nephritis was terminated due to safety concerns and development of veltuzumab for non-cancer indications was discontinued [12]. However, five biologicals targeting BAFF or CD22 are currently undergoing clinical trials for SLE (Table 1) [12]. There are several potential explanations behind the failure of anti-CD20 antibodies and the success of anti-BAFF antibodies, including issues with selection of patients and primary outcomes. Thus, Phase III trials exploring belimumab in SLE selected patients and primary outcome based on careful analysis of the negative Phase II trial [12, 17–19]. An *ad hoc* primary outcome composite index [Systemic Lupus Erythematosus Responder Index (SRI)] was developed. As an alternative hypothesis, there might be genuine differences in the efficacy of B-cell-targeting drugs.

BAFF AND APRIL

BAFF and a proliferation-inducing ligand (APRIL) are TNF superfamily cytokines that share two receptors in B cells (TNFRSF13B/TACI and TNFRSF17/B cell maturation antigen (BCMA)), while BAFF alone binds a third B-cell receptor (TNFRSF13C/B-cell-activating factor receptor (BAFFR)) [20] (Figure 1). BAFF receptors are differentially expressed by B cells at different stages of maturation and are expressed by some non-B cells. BAFFR is required for survival and maturation of immature B cells, TACI for T-cell-independent B-cell responses, negative regulation of B cells and class-switch recombination of B cells and BCMA for increasing plasma cell survival [21, 22].

BAFF and APRIL are expressed by a variety of cell types, although key sources are neutrophils, monocyte/macrophages

Table 1. Selected biologicals under clinical development targeting B-cell trophic factors or B cells in SLE [,]

Drug	Type of drug	Action	SLE clinical status
Targeting BAFF			
Belimumab (Benlysta)	mAb	sBAFF inhibitor	In clinical use
Tabalumab	mAb	sBAFF and mBAFF inhibitor	Phase III
Blisibimod	Peptibody	sBAFF and mBAFF inhibitor	Phase III
Atacicept	TACI-Ig fusion protein	BAFF and APRIL inhibitor	Phase III
Targeting other B-cell trophic cytokines			
Tocilizumab	mAb	IL-6 inhibitor	Phase III
Targeting B-cell membrane antigens			
Epratuzumab	mAb	CD22 antagonist	Phase III

mAb, monoclonal antibody; sBAFF, soluble BAFF; mBAFF, membrane-bound BAFF; Ig, immunoglobulin.

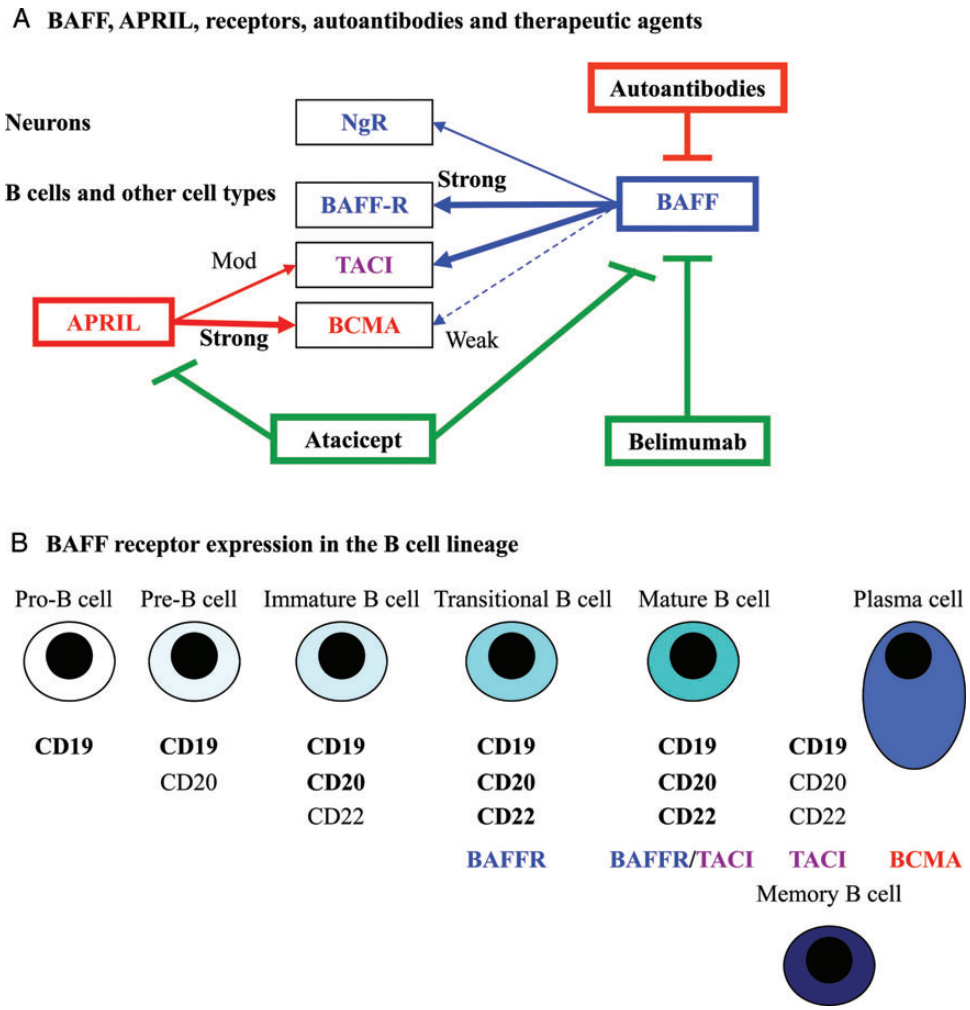

FIGURE 1: B-cell-targeted therapies in SLE: focus on BAFF. (**A**) BAFF, APRIL, receptors, autoantibodies and therapeutic agents. Specificity of BAFF, APRIL, BAFF receptors, BAFF autoantibodies and key therapeutic BAFF-targeting agents [20]. Strong, moderate (mod) and weak refer to the strength of the ligand–receptor interaction. (**B**) BAFF receptor expression in the B-cell lineage. Expression of cell surface proteins by B cells according to maturation state. CD20 and CD22 are targets of biologicals that, unlike those targeting BAFF, directly bind to B cells.

and dendritic cells (Table 2). BAFF is also expressed in B-cell lineage cells. BAFF may be present at the cell membrane and as a soluble protein. Soluble BAFF is required for B-cell homeostasis. In contrast, APRIL is only found as a soluble protein, although a protein comprising the intracellular portion of TWEAK and the extracellular portion of APRIL (TWEPRIL) may be present in the cell membrane [20].

BAFF promotes survival and differentiation of B cells and allows activated autoreactive B cells to escape negative selection [20, 23, 24]. Additional functions beyond B-cell biology include the regulation of activation of self-reactive T cells [20]. Unravelling these additional functions may impact on our understanding of the mechanisms of action and potential complications of BAFF-targeting therapies and of SLE pathogenesis

Table 2. Some key cells expressing BAFF, APRIL or BAFF/APRIL receptors [ ]

Ligand	Cell type	BAFF receptor			
Leucocytes					
	Immature B cells	BAFFR			
BAFF, APRIL	Mature B cells	BAFFR	TACI		
	Plasma cells			BCMA	
BAFF, APRIL	Activated T cells	BAFFR			
BAFF, APRIL	Neutrophils, monocytes/macrophages, dendritic cells				
Other cell types					
	Neurons				Nogo-66 receptor (NgR)
BAFF	Microglia	BAFFR	TACI		
BAFF, APRIL	Adipocytes	BAFFR	TACI	BCMA	
BAFF, APRIL	Keratinocytes	BAFFR	TACI	BCMA	
BAFF, APRIL	Adipose tissue-derived stem cells	BAFFR	TACI	BCMA	
BAFF, APRIL	Tumour cells[a]	BAFFR	TACI	BCMA	

[a]Features from different tumours summarized.

[20, 25, 26]. There is evidence that BAFF contributes to the pathogenesis of SLE [21]. BAFF overexpressing mice develop autoantibodies and tissue injury reminiscent of human SLE [27], circulating BAFF levels may be increased in SLE patients, especially in those with central nervous system and kidney involvement and some studies suggest that may predict an increase in SLE activity [21, 28, 29], and belimumab decreases SLE activity [18, 19]. Interestingly, African American patients with SLE have higher BAFF levels regardless of disease activity [30]. This should be taken into account when interpreting belimumab trial results and anti-BAFF autoantibody data.

APRIL promotes survival of long-living plasma cells [21]. However, APRIL overexpression in mice does not lead to autoimmunity and targeting APRIL was not universally effective in animal SLE models. Serum APRIL levels have been found to be increased in autoimmune diseases, but an inverse correlation with serum BAFF, anti-dsDNA titres and clinical disease activity was also reported [21, 31].

BELIMUMAB

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human BAFF that blocks the binding of soluble BAFF to its receptors. Thus, contrary to anti-CD20 or anti-CD22 antibodies, belimumab does not bind B cells directly. Belimumab does not acutely deplete B cells but decreases B-cell survival and reduces the differentiation of B cells into immunoglobulin-producing plasma cells. Long-term (3 years) belimumab treatment decreased by 60–90% naïve and activated B cells and plasmacytoid and plasma cells and by 20–30% IgG levels [32].

EMA licensed belimumab as add-on to standard therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy [2]. Belimumab is administered intravenously initially every 2 weeks for 1 month and monthly thereafter. Therapy is reconsidered if there is lack of improvement within 6 months. Some patients have been on belimumab for 7 years [33]. Owing to lack of studies it is not recommended for patients with severe active lupus nephritis or central nervous system lupus, or in combination with other B-cell-targeted therapy or intravenous cyclophosphamide.

Ongoing belimumab trials are completing clinical development of SLE and exploring efficacy in preventing kidney transplant rejection and treating membranous nephropathy, diffuse cutaneous systemic sclerosis and immune thrombocytopenia [34]. A recently completed Phase II randomized controlled trial (RCT) in Sjögren's syndrome was more promising than the one in rheumatoid arthritis.

Three major trials of belimumab in SLE have been reported [18, 19, 33, 35]. A Phase II RCT in SLE patients with disease activity (SELENA-SLEDAI score >3) and a history of autoantibodies failed to meet its primary end point [35]. Subgroup analysis disclosed that the SELENA-SLEDAI score significantly improved in patients who were autoantibody positive at baseline and allowed to define a novel SRI resulting from a combination of pre-existing scores [12, 17]. Two Phase III trials (BLISS-52 and BLISS-76) randomized autoantibody positive patients with active disease (SELENA-SLEDAI >5) at baseline despite standard of care to addition of belimumab or placebo [18, 19]. The trials differed in their geographic and ethnic composition and were heterogeneous in terms of efficacy. The reasons behind the differences in response rate merit further studies. Belimumab appeared to be less efficacious in BLISS-76, which enrolled mainly US patients [19]. This trial met its primary end point at 52 weeks, but failed to show differences at 76 weeks [19]. Pooling both trials, the difference in the SRI response rate of belimumab versus placebo was 12% (51 versus 39% responses) [2, 33]. *Post hoc* analysis showed a higher advantage (19%) over conventional therapy for patients with both low complement and positive anti-dsDNA at baseline. At Week 52, belimumab reduced severe flares (30 to 19%) and resulted in higher rates of normalization of high IgG levels or low C3 and C4 and of negativization of anti-dsDNA antibodies [36].

Although promising, additional experience should definitely find the place for belimumab in SLE therapy. In addition to the modest therapeutic effect, the differences in efficacy in the two Phase III trials and the lack of studies in more severely affected patients, the FDA noted the non-significant higher exposure-adjusted risk of death (placebo 0.43, belimumab 0.73) and the hint of lower efficacy and higher toxicity for African and native Americans [36]. More recently, a case of progressive multifocal leukoencephalopathy was described in a SLE patient on belimumab [37].

ADDITIONAL BAFF-TARGETED THERAPIES IN SLE

As of 23 September 2013, BAFF inhibitors were the family of drugs with most ongoing or planned trials in SLE, ahead of immunosuppressive drugs and interferon type I antagonists [12]. Ongoing Phase III trials are evaluating the BAFF inhibitors tabalumab and blisibimod, and the expanded usage or safety of belimumab in SLE [12]. BAFF inhibitors have different targeting specificities that may theoretically result in different therapeutic profiles. Belimumab only binds to soluble BAFF [38], tabalumab and the peptibody (Fc conjugated to a peptide) blisibimod bind both soluble and membrane-bound BAFF [39] and the TACI-Ig fusion protein atacicept binds both BAFF and APRIL. Thus, tabalumab and atacicept may result in a more complete blockade of BAFF signalling [12]. A Phase II/III atacicept trial in lupus nephritis treated with mycophenolate was terminated due to increased risk of serious infections, while a Phase IIb trial is exploring subcutaneous atacicept for SLE [40, 41]. In contrast, tabalumab safety was acceptable in rheumatoid arthritis [39] and blisibimod was safe and efficacious in a Phase II trial in SLE, reducing albuminuria [42].

BAFF-BINDING AUTOANTIBODIES IN SLE

In a recent *Journal of Clinical Investigation* paper, Price *et al.* [3] used serum factor arrays containing 160 analytes to identify targets of autoantibodies in serum from 30 individuals with SLE and 15 healthy controls. SLE patients had an interferon-high ($n = 15$) or a interferon-low signature ($n = 15$) as defined by gene expression microarrays in whole blood displaying high or low levels of type I interferon-regulated mRNA transcripts [43]. The array technique identified in SLE patients IgG autoantibody reactivity to novel cytokine, chemokine and growth factor antigens, including BAFF, as well as to known SLE autoantigens (Table 3). The autoantibody profile of SLE differed from two syndromes of human immunodeficiency associated with autoreactivity to cytokines: autoimmune polyendocrine syndrome type (APS-1) and recurrent disseminated mycobacterium avium complex (DMAC) [3]. The presence of BAFF reactivity was validated by enzyme-linked immunosorbent assay (ELISA) in the same SLE and control samples and in 93 additional SLE samples. ELISA detected BAFF reactivity above the highest value found in controls in 6/30 (20%) and 13/93 (14%) SLE patients from each cohort.

Table 3. Prototypical SLE autoantibody targets and novel serum factor antigens targeted by autoantibodies found in sera from individuals with SLE by a novel human serum factor protein microarray [ ]

Prototypical SLE autoantibody targets
Histones
Single- and double-stranded DNA
Topoisomerase I (Scl-70)
Components of the U1 small nuclear ribonucleoprotein RNA splicing complex
Connective tissue antigens
Novel serum factor antigens targeted by autoantibodies in SLE
TNF superfamily cytokines: BAFF, TNF
TGF-β1–TGF-β3
Interleukins: IL-2, IL-15, IL-23
Interferons: interferon-α2B, interferon-γ
Growth factors: EGF, growth hormone

IgG from SLE samples reactive to BAFF prevented BAFF-induced signalling in cultured cells, suggesting that autoantibodies interfere with BAFF function just as therapeutic anti-BAFF monoclonal antibodies do. However, results were not clear-cut. There was considerable overlap in the blocking activity of IgG from samples with high and low anti-BAFF binding levels. Moreover, BAFF signalling blocking activity was present in IgG from healthy controls, but not in SLE patients with low anti-BAFF binding levels. Although the number of samples subjected to these functional studies was low, this raises the possibility that low neutralizing anti-BAFF activity in some SLE patients is abnormal. Indeed, anti-BAFF autoantibody levels assayed by ELISA were lower in SLE patients with low anti-BAFF levels than in controls.

Serum BAFF concentrations in these SLE patients (mean around 1000 pg/mL, range: 500–3500 pg/mL) were within the lower range that could be detected by the cell culture functional assay and there were no differences in mean BAFF concentrations between anti-BAFF-high and anti-BAFF-low samples. However, the ability of anti-BAFF-high and anti-BAFF-low serum to activate the BAFF receptor was not tested and the relative blocking capacity of autoantibodies compared with belimumab was not explored. Thus, the overall functional significance of the interplay between circulating BAFF and anti-BAFF autoantibodies remains unclear.

The significance and functional consequences of anti-BAFF antibodies in control subjects and of the higher and lower than control values found in SLE patients should be viewed in the context of two cytokines, BAFF and APRIL, that may activate four different receptors, some of them shared between them. Anti-cytokine antibodies and other evidence of low-level, subclinical autoimmunity occur in normal subjects [44, 45]. However, neutralizing anti-cytokine autoantibodies may have pathological consequences. Thus, anti-interferon-γ autoantibodies are thought to interfere with Th1-mediated immune responses and predispose to chronic recurrent mycobacterial infections in conditions such as DMAC [46]. In SLE, anti-interferon-α autoantibodies were associated with decreased interferon-pathway and disease activity while anti-G-colony-stimulating factor autoantibodies were associated with neutropenia [47, 48]. However, interferon-α autoreactivity as detected by the current array assay was associated with a high interferon signature [3], suggesting potential heterogeneity in the specificities and activities of autoantibodies. Unfortunately, no information was provided on the association of anti-BAFF reactivity with race or clinical or routine analytical data reflecting severity or activity of disease, such as SLEDAI or anti-DNA or complement levels, that have been shown to be associated with response to therapeutic anti-BAFF antibodies. Median SLEDAI (four and two for the two cohorts) place most patients studied in this report outside the population for whom therapeutic anti-BAFF strategies may be indicated. Furthermore, there was no information on type or timing of therapies received. Thus, it is

too early to draw conclusions on whether determination of anti-BAFF autoantibodies may provide insights into the variable efficacy of therapeutic anti-BAFF strategies, which appears to depend on both baseline severity of SLE and on poorly characterized ethnic and geographical factors.

Preliminary studies in 30 SLE patients suggested a positive association between BAFF reactivity and a high interferon signature, which, in turn, is associated with severity of disease, higher autoantibody and circulating cytokine levels and lower representation of Caucasians [43, 49–51]. BAFF reactivity was also positively associated with circulating levels of 11 out of 168 (6.5%) serum factor proteins tested in 30 SLE patients. These included cytokines to which autoreactive antibodies were identified, such as TNF and IL1, as well as ICAM3 and CCL3. The latter two (2/11, 20%) were among the 10 circulating analytes found to have higher levels in interferon-high patients than in interferon-low patients. Thus, there is a minor overlap in the circulating analyte profile of BAFF reactive SLE patients and interferon-high patients. Whether anti-BAFF positive patients represent a different form of SLE than interferon-high patients with implications for course of the disease, outcomes or therapeutic response is unknown. It would be interesting to test the potential relationship between autoreactive anti-BAFF antibodies and a hypothetical BAFF-signature of genes regulated by BAFF, as well as to features of long-term belimumab-induced changes in B cells.

STANDING RESEARCH QUESTIONS ON BAFF AND SLE

The report by Price *et al.* [3] (Table 4) illustrates the complexities of SLE and the gaps in our current understanding of the disease pathogenesis and therapy. Further research is needed to unravel the potential contribution of anti-BAFF antibodies to the pathogenesis of SLE and their biomarker potential regarding specific forms of SLE, outcomes or response to therapy. What triggers autoreactivity to cytokines? Are anti-BAFF autoantibodies a further manifestation of autoimmunity without a specific functional relevance? Is there a relationship between anti-BAFF autoantibodies and severity of disease or kidney flares? Will patients with autoantibodies to BAFF respond differently in terms of efficacy or adverse effects of belimumab? In this regard, can anti-BAFF antibodies be both a therapy for SLE and a pathogenic mechanism of the disease? What is the meaning of naturally occurring anti-BAFF autoantibodies in healthy controls? Are lower-than-control anti-BAFF autoantibody levels found in some SLE patients pathological? Price *et al.* [3] discuss unpublished observations of increasing BAFF-targeted autoantibodies over time in experimental SLE, suggesting that BAFF autoreactivity is not exclusive of human SLE. The availability of an animal model may help unravel the significance of BAFF-targeted autoantibodies.

The potential clinical use of the high-throughput array technology that allowed identification of anti-BAFF antibodies also merits discussion. The sensitive (1–2 μL serum) protein microarray could eventually be used for clinical patient profiling once patterns that associate with certain pathogenic mechanisms, disease outcomes or response to therapy are defined [3].

Table 4. Key messages

The B-cell survival and maturation factor BAFF is thought to be a key mediator of SLE
The neutralizing anti-BAFF monoclonal antibody belimumab is licensed to treat SLE without severe nephritis
However, SLE is also characterized by the presence of circulating neutralizing anti-BAFF autoantibodies
Anti-BAFF autoantibodies correlate with some features associated to SLE severity
Further studies are needed to understand the potential contribution of anti-BAFF autoantibodies to the pathogenesis of SLE or their biomarker potential to stage the disease or predict outcome or response to therapy

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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