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ANTI-BLYS BIOLOGICS IN THE B-CELL TARGETED THERAPY OF SYSTEMIC LUPUS ERYTHEMATOSUS: FOCUS ON EFFICACY AND SAFETY OF BELIMUMAB, ATACICEPT AND TABALUMAB.

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disease characterized by formation of autoantibodies from B cells that target an array of self-antigens. B cells remain a prominent target for intervention, in which targeting B cell survival factor BLyS is the most efficient, as elevated BLyS levels are associated with greater disease activity in SLE. Though, there are conventional therapies available, advent of anti-BLyS biologics raised the potential of SLE treatment with the approval of belimumab. This review critically analyzes efficacy and safety of anti-BLyS biologics; belimumab, atacicept and tabalumab. Belimumab, a fully humanized monoclonal antibody, binds soluble BLyS and inhibits its biological activity. The potential of belimumab to improve disease activity, reduce flares, increase steroid withdrawal and improve overall quality of life is certainly a momentous breakthrough in lupus community. In contrast, atacicept, a recombinant fusion protein is capable of preventing BLyS binding with B cell receptors, thereby modulate autoreactive B cell function. Higher dosages of atacicept is well tolerated and shows a beneficial effect on SLE patients' clinical outcome. Tabalumab, a high-affinity human monoclonal antibody is directed against both membrane and soluble BLyS to obtain optimal therapeutic effect. The promising pharmacodynamics effect and steroid withdrawal shows the potential of tabalumab to uplift SLE patients' clinical outcome. Thus, belimumab cannot be considered as the most efficacious, since there remains a strong suggestion that higher doses of atacicept is effective, while tabalumab is proficient in targeting both soluble and membrane BLyS.

Keywords: Systemic lupus erythematous, B cells, autoantibodies, BLyS, anti-BLyS biologics

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multifactorial chronic inflammatory autoimmune disease, with evidence of genetic and environmental effects (Tang et al., 2010; Alarco´n-Segovia et al., 2005; Arbuckle et al., 2003). It is characterized by aberrations throughout the immune system resulting in a diverse autoantibody production, immuno-inflammation and end organ damage (Nightingale et al., 2017; Houman et al., 2004; Bae et al., 2001). In 1950's SLE was thought to be rare, however studies conducted in USA between 1950 and 1992 reported a higher incidence (Uramoto et al., 1999). Estimated clustering of annual SLE prevalence values between 3.2 – 517.5 per 100, 000 of global population, with higher incidence in women and non-white ethnic groups (Fatoye, Gebrye and Svenson, 2018; Izmirly et al., 2017; Rees et al., 2017; Carter, Barr and Clarke, 2016; Nasonov et al., 2014). The global SLE

prevalence is shown in Figure 1, with variations in several countries due to different ethnic groups, gender and genetic makeup (Table 1) (Lim et al., 2014; Somers et al., 2014; McCarty et al., 1995).SLE incidence is common in women due to the influence of the sex hormones estrogen and prolactin (Bynoe, Grimaldi and Diamond, 2000). Moreover, studies of Deshapriya (2018), estimated 90.3% of SLE prevalence within reported autoimmune disease patients, of rheumatology clinics in Sri Lanka.

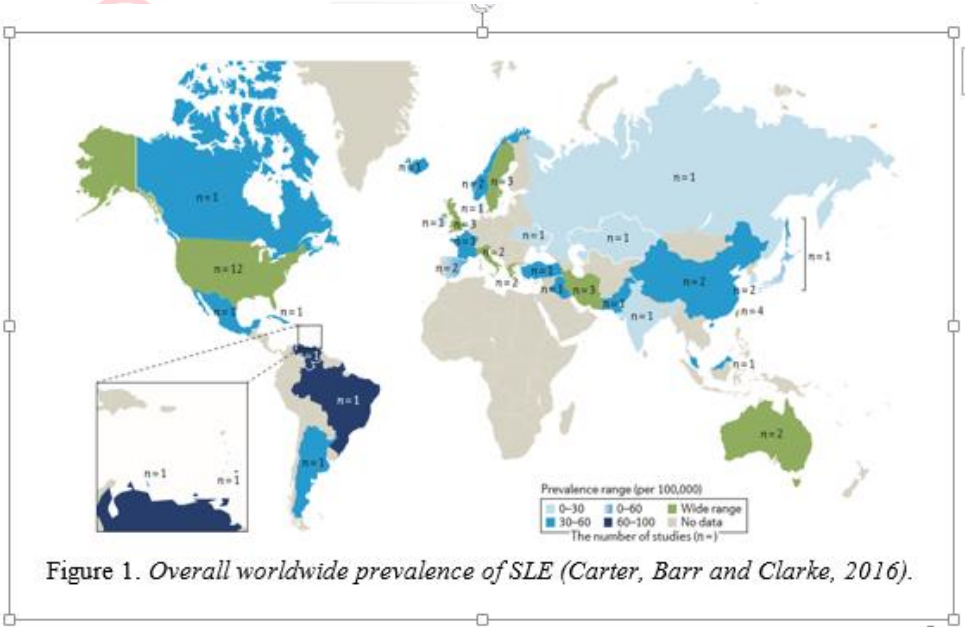


Figure 1. *Overall worldwide prevalence of SLE (Carter, Barr and Clarke, 2016).*

Table 1. SLE prevalence by country.

Region	Country and study period	Prevalence range (per 100,000 of the population)			Authors
		Overall	Males	Females	
Asia	Taiwan, 2003-2008	37.0–97.5	8.4–28.5	66.6–179.4	Yeh *et al*. (2013)
	India, 1972-1993	3.2	N/D (ratio 1:1.2)		Malaviya *et al*. (1993)
	South Korea, 1989-2010	18.8–26.5	5.5–7.5	35.7–45.8	Shim *et al*. (2013)

	Malaysia, 1974-1990	43.0	N/D (ratio 1:12)		Wang *et al*. (1997)
Europe	United Kingdom, 1999-2012	24.0–517.5	3.7	35.0–177.0	Rees *et al*. (2017)
	France, 2008-2010	47.0	1.78	9.11	Arnaud *et al*. (2014)
	Greece, 1982-2001	39.5–110.0	9.5	69.3	Alamanos *et al*. (2003)
	Ireland, 1992-1993	25.4	N/D (ratio 1:11)		Gourley, Patterson and Bell (1997)
	Denmark, 1995-2003	21.9–28.3	N/D (ratio 1:10)		Laustrup *et al*. (2009)
	Norway, 1999-2008	44.9–51.8	9.7–10.7	89.3–91.0	Lerang *et al*. (2012)
	Ukraine, 2010	14.9	3.7	23.8	Nasonov *et al*. (2014)
North America	USA, 1950-1992	42.0–300.0	4.4–54.0	45.0–408.2	Uramoto *et al*. (1999)
South America	Brazil, 2000	98.0	90.0	110.0	Vilar and Sato (2002)
	Mexico, 1993-1995	60.0	40.0	80.0	Walsh *et al*. (2001)
Middle East	Turkey, 1998-2002	59.0	12.0	104.0	Cakir *et al*. (2012)
N/D – No Data					

Clinical heterogeneity of SLE develops more frequently with severe disease course instigating more organ damage and high mortality (Figure 2). Symptoms such as fatigue, joint pain, photosensitivity and malar rash are non-specific for SLE which can delay disease diagnosis and precede to severe clinical manifestations, resulting in functional impairments that reduce patient activity and productivity (Garris, Shah and Farrelly, 2015). Nonetheless, long term prognosis and disease flares of SLE is

associated with significant health-care costs and diminished quality of life (Garris *et al*., 2013). Therefore, the substantial individual and socioeconomic burden of SLE remains inevitable.

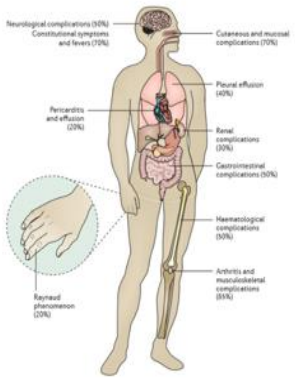


Figure 2. *Clinical heterogeneity of SLE (Kaul et al., 2016).*

Similar to all rheumatic diseases, etiology of SLE is unknown. However, it comprises of environmental factors, which act on permissive genes to trigger SLE progression (Alarco´n-Segovia et al., 2005). More than 50 genes associated with SLE are identified by Genome-wide association studies (GWAS) of missense single nucleotide polymorphisms (SNPs), regardless of geographical areas and ethnicities (Deng et al., 2014). Moreover, National Institute of Environmental Health Sciences (NIEHS) Expert Panel in 2010 identified silica dust exposure as a potential environmental risk factor along with smoking and Epstein Barr virus (EBV) exposure to a lesser extent.

The understanding of SLE pathogenesis has grown drastically in the past decade, resulting in a flare-up in promising targeted therapeutic approaches. B cells act as a critical arm in SLE through antibody dependent and independent manners (Raslan et al., 2018). According to Arbuckle et al. (2003), it is of evident that breakdown of self-tolerance occurs very early in disease progression. Loss of self-tolerance in B cells promotes formation of pathogenic autoantibodies and overactive cell mediated immune response through T cells, dendritic cells and cytokines (Odendahl et al., 2000). Moreover, B cell fate and establishment of tolerance are determined by a transmembrane protein termed B Cell Activating Factor (BAFF), also known as B Lymphocyte Stimulator (BLyS) belonging to the tumor necrosis factor (TNF) family (Nicoletti et al., 2016). Furin protease cleaves transmembrane BAFF and releases soluble BAFF. Binding of soluble BLyS/BAFF to autoreactive B cells via three receptors; B-cell maturation factor Ag (BCMA), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and BR3/BAFF-R, promotes survival and development of B cells (Figure 3) (Nicoletti et al., 2016). Thus, BLyS acts as a promising target for therapeutic intervention of SLE (Petri et al., 2008).

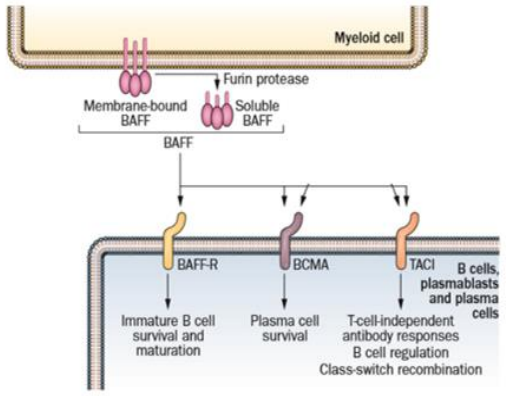


Figure 3. *Role of BAFF in B cell stimulation (Vincent et al., 2014).*

The scope for anti-BLyS biologics has risen with the approval of an anti-BLyS drug by US Food and Drug Administration (FDA) in 2011. However, 45% of patients indicated that the effects of medication impair their daily activities (Lupus Foundation of America, 2014).

Nonetheless, lack of qualified clinical trials and presence of adverse events observed in patients under treatment required the necessity of analyzing efficacy and safety of the present anti-BLyS biologics (Tian et al., 2018). Accordingly, this review utilizes the evaluation of efficacy and safety of three major anti-BLyS biologics, belimumab, atacicept and tabalumab, since development of effective and safer therapeutics is of the essence.

Therapeutic strategies for SLE

Conventional therapeutic strategies and the advent of biologic therapy

The management of SLE, as outlined in the recommendations by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (2018), is about reducing disease activity, preventing disease flares and minimizing drug related adverse events. Conventional therapeutic strategies of SLE includes; non-steroid anti-inflammatory drugs (NSAIDs), antimalarial drugs, corticosteroids and immunosuppressive agents (Table 2). However, only few NSAIDs, corticosteroids and antimalarials are approved by FDA, while most treatments used for SLE are off-label use of medications developed for different autoimmune indications (Iudici et al., 2016; Thamer et al., 2009; Meinao et al., 1996). It appears that, 2000-2010 has been a golden decade for SLE with the introduction of biological therapies which provided scope and excitement for lupus community.

Table 2. Conventional therapeutic strategies of SLE

Drug class	Mechanism of action	Commonly used agents	Dosage	Adverse events
NSAIDs (Shin, 2017)	Produce anti-inflammatory, analgesic and antipyretic effects by blocking prostaglandin synthesis	Aspirin, Ibuprofen	Various dosages	Renal toxicity, hepatic toxicity, hypertension, gastrointestinal irritation and bleeding

Corticosteroids (Davidson *et al.*, 2018)	Decrease inflammatory responses by inhibiting cytokine activation, interleukins, γ-IFN, TNFα	Prednisone Methylprednisolone IV	0.5–2 mg/kg per day 500–1,000 mg daily for 3 to 6 days	Hyperglycemia, hyperlipidemia, osteoporosis, cataracts, edema, muscle weakness, growth suppression
Antimalarials (Tian *et al.*, 2018)	Unclear, thought to inhibit T-cell activation and inhibit cytokine activity	Hydroxychloroquine	200–400 mg daily	Muscle weakness, macular damage
Immunosupressants (Shin, 2017)	Suppression of various immune functions including reduction in B cell and T cell proliferation	Cyclophosphamide, Azathioprine, Mycophenolate	1–3 mg/kg per day	Hepatotoxicity, renal dysfunction, infertility, increased risk of infection and cancer

Biologics are drugs assembled from a living organism or its products, directed to alter cytokine function and facilitate B cell depletion, inactivation and survival blockade (Figure 4) (Bezalel et al., 2012). The only biologic to be approved by FDA is belimumab. While, rituximab entered the realm of clinical practice as an off-label drug for SLE (Ryden-Aulin et al., 2016).

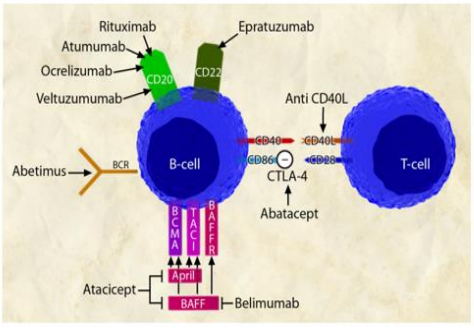


Figure 4. *Novel biologics and their respective targets in the pathogenesis of SLE (Yildirim-Toruner and Diamond, 2011).*

Anti-BLyS Biologics

The significant characteristic of SLE is the presence of broad antibody spectrum. Therefore, targeting B-cell survival and differentiation is a mandatory approach in treatment. Thus, anti-BLyS biologics target BLyS, the survival factor of plasma cells, immature B cells and mature B cells, by affecting B cell growth and differentiation (Yan et al., 2001). Studies of Petri et al. (2008) revealed, elevated levels of BLyS in plasma and peripheral blood of SLE patients. Due to the presence of limitations in conventional therapies, the focus on biologics has arisen recently, providing promising aspects on reducing disease activity and preventing disease flares to improve quality of life. In addition to belimumab, anti-BLyS drugs

such as atacicept and tabalumab are under development (Table 3) (Oon et al., 2018). Belimumab and tabalumab are monoclonal antibodies, derived from the most abundant human G isotype-1 immunoglobulin (IgG1) and IgG4 respectively, which are hydrophilic, large protein molecules with two identical antigen binding regions (Fab) and one crystallisable region (Fc) (Figure 5) (Shin et al., 2018; Manetta et al., 2014). Similarly, atacicept is a recombinant fusion protein with extracellular ligand binding portion of TACI receptor and the Fc portion of human IgG1 (Figure 6) (Pena-Rossi et al., 2009).

Table 3. Anti-BLyS biologics for SLE.

Drug (Study)	Company	Clinical trial/study	Indication	Stage of development
Belimumab (Furie *et al*., 2008; Wallace *et al*., 2009; Navarra *et al*., 2011)	GSK	Phase I Phase II Phase III – 2 trials BLISS-52 BLISS-76	Adult SLE patients with active disease regardless of standard treatment	Marketed
Atacicept (Dall' Era *et al*., 2007; Merrill *et al*., 2017)	Merck Serono	Phase I Phase II/ III – known as APRIL/SLE trial	Non renal SLE patients	Phase III studies – known as ADDRESS trial
Tabalumab (Isenberg *et al*., 2015)	Eli Lily	Phase III – 2 trials ILLUMINATE-1 ILLUMINATE-2	Non renal SLE patients	Phase III study in progress

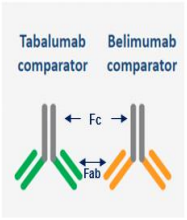


Figure 5. *Schematic diagram of both belimumab and tabalumab (Nicoletti et al., 2016).*

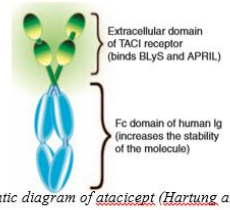


Figure 6. *Schematic diagram of atacicept (Hartung and Kieseier, 2010).*

Efficacy of anti-BLyS biologics are portrayed by the achievement of maximum response in research setting and the presence of therapeutic response in clinical setting. The epitope structure and the precise mechanism of anti-BLyS enables the drug to obtain high efficacy. Along with the clinical benefits on; reducing circulating autoreactive, memory B cells and plasma cells, reducing anti-dsDNA antibody levels and normalization of low complement (C3/C4) levels (Nicoletti et al., 2016; Turner-Stokes et al., 2011; Bossen et al., 2008).

Considering BLyS antagonist mechanism, belimumab binds to soluble BLyS and tabalumab binds to both soluble and membrane BLyS (Witcher et al., 2015; Furie et al., 2008). Atacicept has another anti-BLyS approach, in which it prevents BLyS binding to specific B cell receptors; BAFF-R, BCMA and TACI (Dall' Era et al., 2007). Thus, aforementioned anti-BLyS biologics modulate autoreactive B cell function by hindering its survival and differentiation (Figure 7).

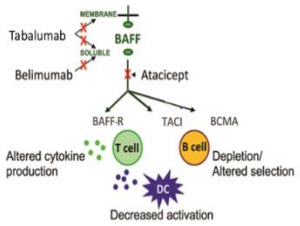


Figure 7. *Mechanism of action for anti-BLyS biologics, belimumab, atacicept and tabalumab (Boneparth and Davidson, 2012).*

According to Telleman and Junghans (2000), the Fc portion of anti-BLyS biologics are essential in determining the pharmacokinetic profile of the drug, which will bind to neonatal Fc receptor (FcRn) of reticuloendothelial cells (RES) and guards the molecule from intracellular catabolism in order to extends its half-life in circulation. The fused IgG1 Fc region of atacicept along with the extracellular antigen binding domain will provide a long half-life and stability to the drug than belimumab and tabalumab (Isenberg et al., 2015).

Furthermore, studies of Kowalczyk-Quintas et al. (2018) elucidates a comparison between the affinity of both belimumab and atacicept to BLyS, in which furin protease function is genetically inactivated and the cells with membrane-bound BAFF are expressed, indicating the binding of both the drugs, with high affinity for atacicept (Figure 8). Since, atacicept possesses 250-fold higher binding affinity to the target BLyS than belimumab as it comprises specifically engineered antigen-binding domains (Isenberg et al., 2015).

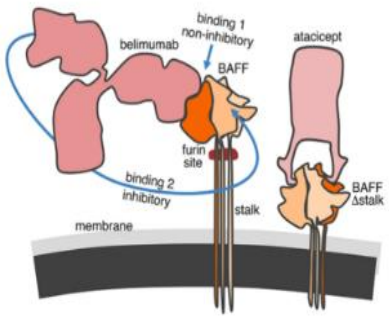
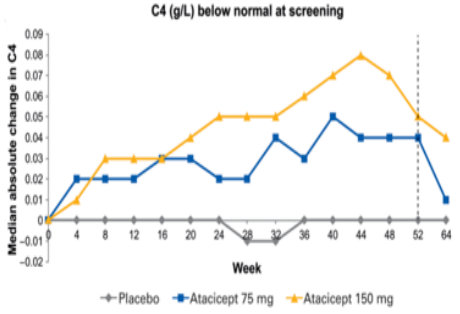


Figure 8. Hypothetical model for belimumab and atacicept binding with membrane BAFF (Kowalczyk-Quintas et al., 2018). Atacicept binds BAFF from the side opposite to the membrane and has free access, regardless of the height of the stalk but belimumab is bulkier and binds more on the side of the BAFF. Also to elicit the function, two inhibitory sites of belimumab should bind with BAFF.

Affinity of tabalumab, measured by Plasmon resonance indicated high affinity for both soluble and membrane BAFF, suggesting that a greater clinical response can be achieved with the inhibition of both BAFF forms instead of either BAFF form alone (Manetta et al., 2014). However, the influence of binding affinity in different clinical outcomes remains indistinct (Shin et al., 2018). Similarly, evaluation of clinical benefits of anti-BLyS is another essential feature to interpret the efficacy of each drug (Table 4).



Efficacy of anti-BLyS mostly depends on its clinical properties. Greater reduction of anti-dsDNA IgG levels in belimumab exhibits the highest effectiveness of the drug (Figure 9) (Biesen et al., 2011). Similarly, atacicept and tabalumab shows higher efficacy than placebo (Figure 10 and 11) (Petri et al., 2013).

Table 4. *Evaluation of clinical properties of belimumab, atacicept and tabalumab.*

Clinical property		Response after 52 weeks of phase III trials		
		Belimumab	**Atacicept**	**Tabalumab**
Sustained reductions in anti-dsDNA levels	Placebo	26%	3%	7%
	Anti-BLyS	**48%**	38%	12%
Normalization of low C3	Placebo	20.8%	4.1%	22%
	Anti-BLyS	**43.5%**	15.4%	37%
Normalization of low C4	Placebo	17.2%	0.4%	22%
	Anti-BLyS	46.4%	**49.5%**	31%
Reductions in B cells (CD20+)	Placebo	7.7%	3%	34%
	Anti-BLyS	**42.9%**	38%	39.9%
Reference		Furie *et al.* (2011)	Isenberg *et al.* (2014)	Miller *et al.* (2015)

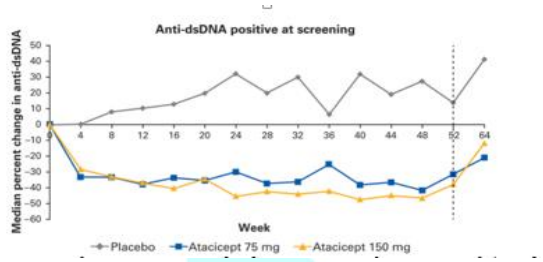


Figure 9. Change in anti-dsDNA IgG in 52 weeks for belimumab phase III trial (Navarra et al., 2011).

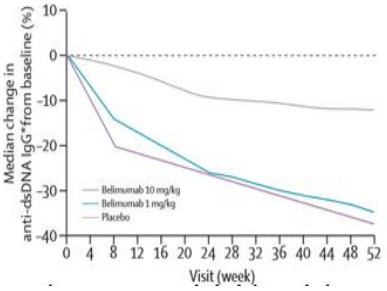


Figure 10. Change in anti-dsDNA in 52 weeks for atacicept phase III trial (Isenberg et al., 2014).

Figure 13. Change in C4 complement concentration in 52 weeks for atacicept phase III trial (Isenberg et al., 2014).

As B cells play a fundamental role in SLE, the major purpose of anti-BLyS is to reduce B cell subsets. Therefore, belimumab and tabalumab being monoclonal antibodies that target BLyS, will inhibit B cell survival and reduce total B cell and plasma cell subsets (Figure 14 and 15) (Merril et al., 2015; Furie et al., 2011). Belimumab shows reduction in several B cell subsets, including active (CD20+/CD69+) and naïve (CD20+CD27−) cells, specific SLE plasma cells (CD19+/CD27BRIGHT/CD38BRIGHT) and short lived plasma cells (Van Vollenhoven et al., 2018). Tabalumab shows significant reduction in mature naïve and memory B cells than placebo (Tanaka et al., 2016).

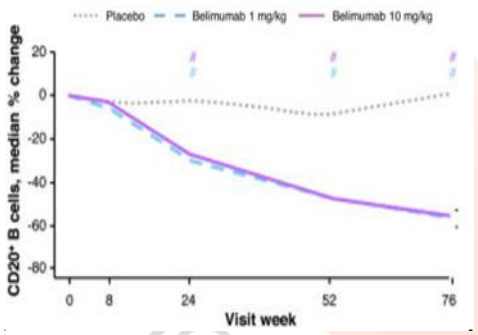


Figure 14. Median percent change in CD20+ B-cell subset for belimumab (Furie et al., 2011).

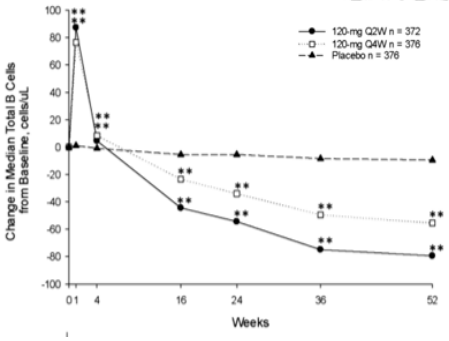
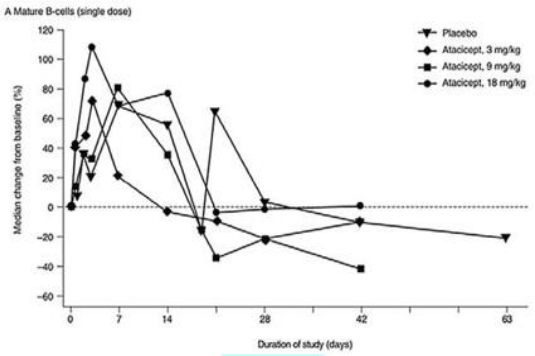


Figure 15. Median change in total B-cell subset for tabalumab (Merril et al., 2015).

Similarly, studies of Pena-Rossi et al. (2009) reported reduction in mature B cells with atacicept. The initial surge in B cell subsets with both tabalumab and atacicept is due to release of memory B cells from secondary lymphoid organs as a homeostatic mechanism to counteract B cell depletion (Figure 16) (Isenberg et al., 2014; Furie et al., 2011).



FFigure 16. Median percent change in mature B-cell counts for single doses of atacicept (Pena-Rossi et al., 2009)

Evaluation of SLE response to treatment

The efficacy of anti-BLyS biologics can be further assessed by the achievement of primary endpoints of SRI, SFI and secondary endpoints of SLEDAI, PGA and BILAG (Table 5) (Castrejon et al., 2014; Thanou et al., 2014; Touma et al., 2011; Yee et al., 2007). These endpoints provide sufficient information on disease burden, renal, musculoskeletal and cutaneous complexity (Petri, Buyon and Kim, 1999). SRI is defined as ≥ 4 reduction in SLEDAI, no new BILAG A or no more than one new BILAG B and no deterioration from baseline in the PGA by

≥ 0.3 points (Ding and Gordon, 2013). Measuring endpoints in SLE treatment revealed a significant impact on increasing treatment efficacy size, accomplishment of low disease activity and demonstration of sustained improvement (Merril et al., 2015; Furie et al., 2011).

Table 5. *Evaluation of primary and secondary endpoints of belimumab, atacicept and tabalumab (Adapted from: Furie et al., 2011; Navarra et al., 2011; Isenberg et al., 2014; Merril et al., 2015).*

Anti-BLyS and placebo	Dose	End points				
		Primary		Secondary		
		SRI	SFI (rate or days for first flare)	SLEDAI (point reduction)	BILAG (no worsening)	PGA (no worsening)
Belimumab	1 mg/kg	40.6%	**70%**	53%	78%	79%
	10mg/kg	**43.2%**	71%	**58%** ≥ 4 point	**81%**	**80%**
Placebo	-	33.5%	80%	46%	73%	69%
Atacicept	75 mg	**55.9%**	54%	58.2%	20.1%	
	150 mg	55.8%	**37%**	**62.7%** ≥ 6 point	**21.4%**	N/D
Placebo	-	41%	58%	42.3%	19.7%	
Tabalumab	120Q2W	**38.4%**	**169 days**	**39%**	**67.7%**	**67.2%**
	120Q4W	34.8%	141 days	35.4% ≥ 5 point	64.4%	62.2%
Placebo	-	27.7%	123 days	27.9%	62.2%	57.2%

N/D – No Data, Q2W- every 2 weeks, Q4W- every 4 weeks, SRI – SLE Response Index, SFI – SLE Flare Index, SLEDAI – Systemic Lupus Erythematosus Disease Activity index, BILAG – British Isles Lupus Assessment Group, PGA – Physician's Global Index

Thus, 10 mg/kg of belimumab met its efficacy endpoints demonstrating a greater SRI with statistically significant ≥4 - point reduction in SLEDAI, no worsening in BILAG and PGA which was the major reason for it to be approved for SLE treatment (Figure 17) (Furie et al., 2011).

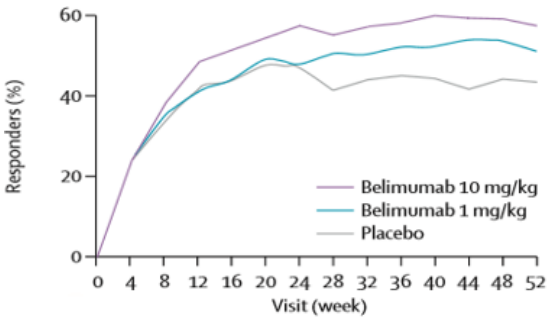


Figure 17. Response to belimumab during 52 weeks assessed with SRI (Navarra et al., 2011).

However, atacicept met its endpoints only with 150 mg dosage, which indicates that only higher doses are effective. Also high-dose treatment is allied with a notably delayed time for first flare (Figure 18) (Isenberg et al., 2014).

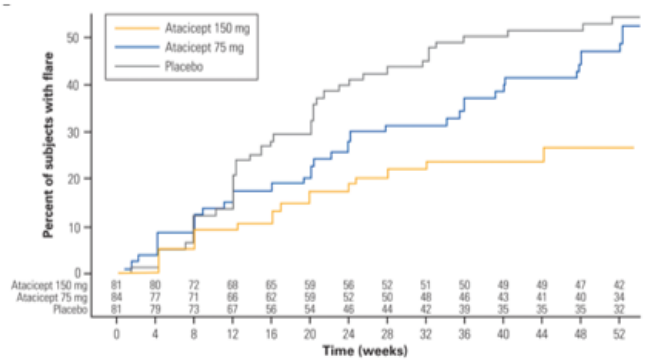


Figure 18. *Time to first new flare in atacicept treated population (Isenberg et al., 2014).*

Tabalumab met its endpoints in 120 Q2W dosage, where it shows high bar for efficacy with ≥5 - point reduction in SLEDAI (Figure 19) (Merril et al., 2015). However, belimumab is the only drug that encountered all the efficacy endpoints.

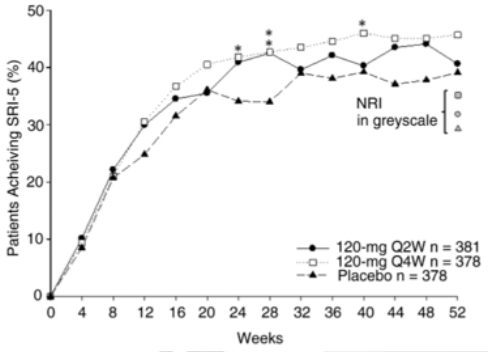


Figure 19. SRI-5 response rates over 52-week tabalumab treatment (Isenberg et al., 2015).

Anti-BLyS: Evaluation of safety

Contraindications

Safety profiles of anti-BLyS mainly focus on the presence of contraindications (Table 6). Considering previous studies, majority of literature indicates belimumab as the safest, in comparison to atacicept. While, tabalumab results in less incidence of contraindications.

Table 6. Evaluation of safety profiles of belimumab, atacicept and tabalumab.

Contraindications		Belimumab	Atacicept	Tabalumab
Serious adverse events (SAEs)	Type	Lupus nephritis Pyrexia Anemia Malignancy	Ventricular bigeminy Arthritis Peripheral edema Paresthesia Pyrexia	Encephalopathy Malignancy Pyrexia
	Percentage	90% had at least one	**98%** had at least one	**45.3%**
Infections	Type	Bronchitis Sinusitis Influenza Tinea pedis Staphylococcal cellulitis Pyelonephritis Herpes zoster	Rhinitis Sinusitis Leptospirosis Pneumonia (*Legionella pneumophila*)	Herpes zoster Tuberculosis Cytomegalovirus Oral candidiasis
	Percentage	37%	**59%**	16.3%
Infusions	Type	Arthralgia (26%) Headache (21%) Rash (21%) Diarrhea (18%) Nausea (18%)	Fatigue Nausea Headache Sore throat Depression	Headache Nausea Back pain Dysphagia Depression
	Percentage	**92%**	78%	82.1%
Laboratory abnormalities	Type	Lymphopenia Prolonged PT	Elevated WBC Low neutrophils	-
	Percentage	20%	Not significant	-
References		Wallace *et al.* (2013) Yamada *et al.* (2013) Furie *et al.* (2008) Navarra *et al.* (2011)	Munafo *et al.* (2007) Dall'Era *et al.* (2007) Nesterov *et al.* (2009) Isenberg *et al.* (2013) Gordon *et al.* (2016)	Isenberg *et al.* (2015) Witccher *et al.* (2015) Rovin *et al.* (2016)

Atacicept shows greater rates of SAEs and infections that lead to two deaths in 150 mg arm, while BLISS-52 trial of belimumab reported nine deaths. Thus, as a cautionary measure APRIL-SLE trial of atacicept was terminated (Furie *et al.*, 2011; Isenberg *et al.*, 2014). However, two deaths were reported with atacicept due to pneumonia, as TACI is involved in diversification of immunoglobulins and when high dosages of atacicept is administered, it may result in significant humoral immune deficiency that instigated lower IgG responses to pneumococcal polysaccharides (Sthoegar *et al.*, 2017; He *et al.*, 2010). Due to absence of significant differences in SAEs between placebo and the drug, tabalumab indicates requirement of further study (Isenberg *et al.*, 2015).

Moreover, atacicept consists of a greater half-life than both belimumab and tabalumab, which can minimize frequent

administration of the drug and prevent toxic development (Table 7).

Table 7. *Pharmacokinetic properties of belimumab, atacicept and tabalumab.*

Parameters	Belimumab (Dose range – 1 to 20 mg/kg)	Atacicept (Dose range of 3–18 mg/kg)	Tabalumab (Dose range of 0.01–8 mg/kg)
Half-life (t½)	8.5–14.1 days	27 to 32 days	1 to 25 days
Clearance (CL)	5.6–7.3 mL/day/kg	2.5-21.0 L/day	2.9-0.1 L/day
Maximum drug concentration (C_{max})	22.3-368.1 µg/mL	15.0-13900 ng/mL	125.301- 357 µg/mL
Reference(s)	Furie *et al.* (2008)	Munafo *et al.* (2007)	Witcher *et al.* (2015)

Anti-BLyS biologics may exhibit linear or non-linear pharmacokinetics, explained by two elimination pathways non-specific cellular elimination and specific target-mediated elimination, respectively (Mould, 2015). The non-specific elimination occurs in RES, which is the intracellular catabolism of the drug that bound to FcRn on the cell surface. This phenomenon tends to be linear as therapeutic concentrations of belimumab will not saturate the amount of FcRn present (Figure 20) (Furie et al., 2008).

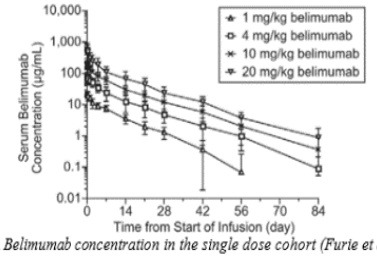


Figure 20. *Belimumab concentration in the single dose cohort (Furie et al., 2008).*

Binding of anti-BLyS to BLyS via Fab region forms drug–target complex, which is eliminated by specific target mediated elimination. Kinetics of drug–target complex is defined by the target-mediated drug disposition (TMDD) model (Levy, 1994). The lack of target mediated elimination could be due to continuous saturation of BLyS by anti-BLyS, which increases drug-target complex concentration and is the major cause for non-linearity (Koch, Jusko and Schropp, 2017). Thus, non-linearity observed in the BLyS–atacicept complex is typical for saturable binding kinetics between the drug and BLyS (Figure 21) (Munafo et al., 2007).

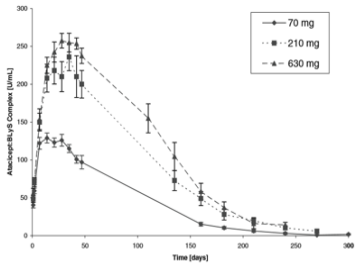


Figure 21. *Atacicept-BLyS complex concentration in single dose cohort (Munafo et al., 2007).*

Similarly, tabalumab shows non-linear pharmacokinetics over 0.01-8 mg/kg doses, with evidence to dose-proportional decline in CL, increase in t½ and greater drug exposure (Figure 22) (Witcher et al., 2005).

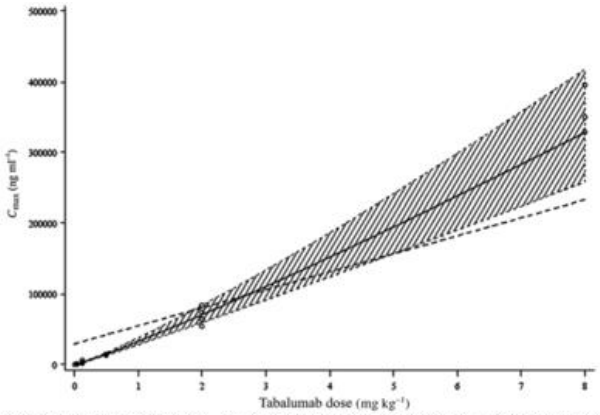


Figure 22. *Dose-proportionality assessment of tabalumab. The solid line denotes the predicted line from the fitted model. The dotted line indicates the predicted line if the PK parameters were dose proportional (Witcher et al., 2005).*

Hence, only belimumab shows linear pharmacokinetics with constant, dose-independent parameters, whereas atacicept and tabalumab shows non-linearity with dose-dependent behavior. This will influence in determining appropriate dose levels and dosing frequency for multiple dosing regimens. Moreover, it is clear that exceeding doses beyond the saturation point will bring about diminishing inhibition of BLyS and toxicity.

Comorbidities: Coping with the quality of life

In comparison to 1950s, though the survival rate of five years for SLE is increased by 40%, and at least one-third of the population have one or more comorbidities that impair their daily activities (Trager and Ward, 2001). Studies of Zonana-Nacach *et al.* (2000), revealed that usage of corticosteroids and immunosupressants during the early stages of SLE will elevate incidence of comorbidities in patients, such as osteoporosis, atherosclerosis and malignancies (Chan *et al*., 2016). Thus, minimizing the usage of corticosteroids and immunosupressants will elevate the life expectancy and quality of life in SLE patients.

Consequently, anti-BLyS biologics has shown promising outcomes in corticosteroid withdrawal in SLE patients, known as the steroid sparing effect (Table 8) (Oon *et al.*, 2018). Belimumab, atacicept and tabalumab shows greater steroid sparing effect than placebo, which in turn can minimize progression of comorbidities in patients and increase the quality of life. In spite of the SAEs caused by atacicept and tabalumab, there remains a strong suggestion that steroid sparing effect can bring about promising outcomes in SLE patients.

Table 8. *Comparison of steroid sparing effect of belimumab, atacicept and tabalumab.*

Anti-BLyS (Dosage)	**Steroid sparing effect**								
	Belimumab			**Atacicept**			**Tabalumab**		
	1 mg/kg	10 mg/kg	Placebo	75 mg	150 mg	Placebo	120 Q2W	120 Q4W	Placebo
	21%	**28%**	12%	**32%**	**27%**	12%	**23.4%**	17.5%	18.9%
Reference	Navarra *et al.* (2011)			Isenberg *et al.* (2014)			Isenberg *et al.* (2015)		

CONCLUSION

In conclusion, anti-BLyS biologics target the key pathogenic process in SLE by preventing BLyS function and autoreactive B cell survival. Better understanding of efficacy and safety profiles of belimumab, atacicept and tabalumab is essential for clinical validation of the drug. In terms of efficacy related to epitope structure and fusion protein, atacicept shows greater effectiveness than the monoclonal antibodies belimumab and tabalumab. With regard to the anti-BLyS mechanism of action, targeting both soluble and membrane BLyS through tabalumab shows greater efficacy than targeting either one alone by belimumab or atacicept. However, in consideration of clinical properties, belimumab is superior to both atacicept and tabalumab. Similarly, from the SLE response to treatment point of view, belimumab shows the highest efficacy with the fulfillment of all the endpoints, while higher dosages of atacicept and tabalumab shows greater efficacy than placebo.

Considering safety profiles, with regarding to pharmacodynamics, belimumab shows the accepted least occurrence of contraindications than atacicept. However, there remains a strong suggestion that, despite the SAEs, pharmacokinetic profile of atacicept shows low toxic response than belimumab and tabalumab. Even though there were no significant differences in contraindications caused by tabalumab and placebo, in comparison to both belimumab and atacicept the incidence of contraindications was less in tabalumab.

Moreover, knowledge regarding pharmacokinetics of anti-BLyS is crucial in determination of precise dosages that can improve SLE treatment on clinical outcomes. Focusing on improving the quality of life in SLE patients by reducing comorbidities, is evaluated with the steroid sparing ability of the drug, in which all three anti-BLyS biologics show significant steroid sparing ability. In addition, proper optimization of clinical trials and necessity of treat-to-target approaches are essential to recognize the complete efficacy and safety profiles of biologics with reduction in present drawbacks.

The use of anti-BLyS is emerging with wide acceptance globally. Even though, belimumab is the only anti-BLyS drug to be approved by FDA, the effect of the drug is not as potent as that of atacicept and tabalumab. Thus, there remains a strong notion that both atacicept and tabalumab are also eligible for the approval with requirement of further studies, since higher dosages of atacicept being effective and tabalumab being a potential to target both soluble and membrane BLyS with greater therapeutic response.

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