REVIEW ARTICLE

# B Cell-Activating Factor (BAFF) and Ubiquitin Enzyme A20 as Functional Proteins in Targeted Therapy on Patients with Systemic Lupus Erythematosus

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## Abstract

**BACKGROUND:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by inflammation. The pathogenesis of SLE involves key proteins, including B cell-activating factor (BAFF) and the ubiquitin enzyme A20, both serving as negative regulators of inflammation and contributing to B cell homeostasis. In this review, focused on interventions directed at BAFF and the A20 enzyme, utilizing monoclonal antibodies either independently or in conjunction with conventional therapy for SLE patients.

**METHODS:** A literature search was conducted on the PubMed platform by combining various terms, including "B-cells activating factor", "TNFAIP3 protein (human)", "therapeutics" or "drug therapy", and "lupus erythematosus, systemic" (limited to the last 10 years). From total of 104 articles discovered in thr search, the total number of articles collected after being filtered was 27 articles.

**RESULTS:** Clinical development and evaluation have been conducted regarding the use of appropriate therapy for SLE patients. Selective BAFF inhibitor has been tested in clinical trials as a blocking agent in BAFF receptor (BAFF-R) and signaling nuclear factor-kappaB (NF-κB) by A20 bindings to inhibit the activation of autoreactive B cells. Just like other antimonoclonal therapies, BAFF and the A20 enzyme can be used as therapeutic targets with a single use or combined with the standard therapy in patients with SLE. In addition, the use of BAFF and A20 also shown to have safe side effects in patients with SLE.

**CONCLUSION:** BAFF protein and A20 enzyme present promising therapeutic targets for managing autoimmune diseases like SLE. Therapeutic interventions can be administered individually or in conjunction with standard treatments.

**KEYWORDS:** systemic lupus erythematosus, therapeutic targets, BAFF, A20

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects numerous organs with a wide range of clinical manifestations.(1–3) SLE is characterized by the development of antibodies that attack body's tissues which further affect multiple organ systems.(4,5) The progression of SLE disease is very complex, and it is characterized by the disappearance of immunological tolerance; therefore, it is difficult to make a diagnosis. Immunological targets or autoantigens involve cell core components, such as double-

stranded DNA (dsDNA), proteins (including chromatin and RNA), and residue of excessive apoptosis on the cell surface that causes self-reactive attacks. Therefore, lymphocytes were simultaneously activated by autoreactive antibodies, resulting in the expansion of inflammatory cells in various organs and comorbidities in SLE disease. (2) The incidence of SLE in the Asia-Pacific ranges from 0.9 to 3.1 per 100.000 people per year, with a prevalence of 4.3–45.3 per 100.000 people annually.(3) Sex is also a crucial risk factor in cases where there are more women than men, attacks at the productive age. SLE is a disease with very high morbidity and mortality rates due to disease progression and treatment.(6,7)

SLE management is complicated since the biological heterogeneity between the patients and the lack of safe and specific therapeutic findings. Therefore, molecular and genetic approaches become a solution in determining the therapy for autoimmune diseases, such as SLE.(7)

The highly complex pathophysiology of SLE involves genetic, hormonal, and environmental factors, as well as autoantibody systems, which results in disease development and activity. Presence of cytokines, such as interferon (IFN), becomes a marker for SLE patients with severe comorbid diseases and manifests, especially in renal, hematologic, neurological, and cardiovascular diseases.(8,9)

Excessive expression of protein, such as B cell-activating factor (BAFF), can become a marker of atherosclerosis where BAFF introduces cell replacement and humoral autoimmunity and increasing of immunoglobulin M anti-oxidized low-density lipoprotein (IgM anti-ox LDL).(10–12) Serum BAFF Levels were significantly associated with the incidence of SLE which is depicted by The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score.(13) The A20 enzyme which functions by regulate the immune response mediated by the nuclear factor-kappaB (NF-κB). The expression of A20 has been established as a negative regulator of NF-κB transcription factor which NF-κB signaling is regulated by B cell receptors in the processes of activation, development, and differentiation of cells.(14,15) The reduction of A20 expression may increase NF-κB signaling in proinflammatory cytokine activators.(16)

BAFF and enzyme A20 through NF-κB signaling have an important role in B-cell maturation and proliferation. B-cell maturation through BAFF binding with BAFF receptor (BAFF-R). BAFF-R stimulation sequesters TRAF3 resulting in NF-κB inducing kinase (NIK) stabilization and NF-κB effector molecule (NEMO)-independent activation of the IκB kinase (IKK)1 complex. Meanwhile, B cell proliferation through B cell antigen receptor (BCR) binding through the activation of the inhibitors of IKK complex containing NEMO resulted in nuclear translocation of the NF-κB dimer. It can be concluded that the NF-κB signaling system mediates the function of BAFF in both maturation and proliferation of B cells. B cell activation by involving CD40 and BAFF-R which is a family of tumor necrosis factor receptor (TNFR).(17)

SLE treatment aims to control disease activity, prevent organ damage, and observe patients for comorbidities, toxicity, and quality of life. The standard treatment for SLE patients with moderate to severe conditions is to use a high dose of corticosteroids, immunosuppressive agents, and cytotoxic agents that have been shown to be effective in reducing organ damage but can cause severe side effects. (3,18) Therefore, it is necessary to find more specific therapy with minimal toxic effects. A therapy that targeting proteins involved B cells and cytokine is an achievement in SLE treatment. The loss of immune tolerance causes the activation of B- and T cells, which become autoreactive as antigen-presenting cells (APC) secreting various proinflammatory cytokines. Differentiation of B cell into plasma blast that secretes antibodies and pathogenic plasma cells and causes inflammation.(3) In this review, we focused on SLE treatment, which targeted BAFF, and the A20 enzyme pathway that plays a role in SLE pathogenesis, both as single therapy or in combination with standard therapy.

## Methods

In collecting the data, PubMed platform was used to search the combination of several terms, such as “B cells Activating Factor” [Mesh]) OR “TNFAIP3 protein, human” [Supplementary Concept]) OR “Tumor Necrosis Factor alpha - Induced Protein 3” [Mesh]) AND “Therapeutics” [Mesh]) OR “Drug Therapy” [Mesh]) AND “Lupus Erythematosus, Systemic” [Mesh]. The chosen articles were Randomized Controlled Trials (RCT) and systematic reviews, and were limited for publications in the last 10 years. Total of 104 articles were discovered in this search, which was then filtered to 83 articles reporting studies using therapeutics targeting BAFF protein and A20 enzyme in human trials. The titles and abstracts of all studies were examined, and full-text versions of publications were reviewed. Later, non-significant articles were excluded, such as articles not targeting BAFF and A20 enzyme (BAFF and A20 inhibitor) and non-specific articles and manuscripts. The total number of articles collected was 27 articles (Figure 1).

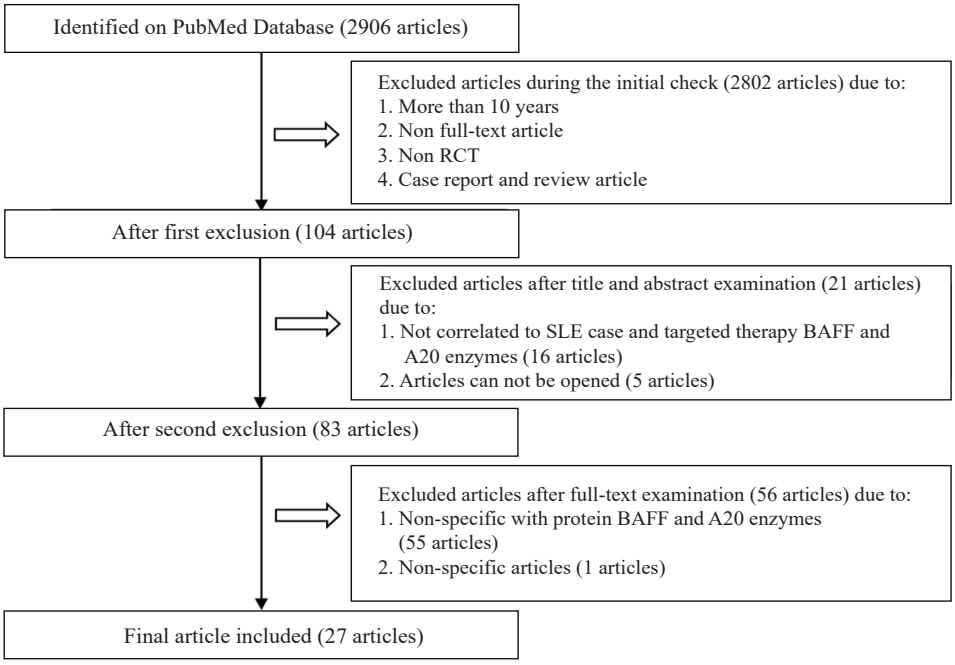


**Figure 1. Flowchart of the literature search process.**

## Results

In the past few years, clinical development and evaluation have been conducted regarding the use of appropriate therapy for SLE patients. However, SLE patients have wide and variative clinical manifestations; as a result, it affects the success rate of therapeutic agents in clinical trials. Specific therapy administered to SLE patients becomes interesting since there have been reports of side effects that affect SLE comorbidities, such as cardiovascular and reduced kidney function up to 60%. Selective BAFF inhibitor has been tested in clinical trials as a blocking agent in BAFF-R and signaling NF-κB by A20 bindings to inhibit the activation of autoreactive B cells.

The goal of administering therapy to SLE patients is to enhance their quality of life. Key factors to consider include the percentage of improvement over time, the duration of the disease, and effective protection against organ damage. The efficacy of therapies targeting BAFF and A20 is detailed in Table 1. This table shows that the use of antimonoclonal therapy, either alone or in combination with conventional therapy, shows improvement in the condition of SLE patients and safety in organ function. Several studies have been conducted comparing BAFF inhibitors therapy and A20 with standard therapy administered to SLE patients. It also uses the same standard combination therapy targeting B cell inhibitors, which can be seen in Table 2.

## Discussion

**BAFF: The Function and Association with SLE**

BAFF is a member of tumor necrosis factor (TNF) and role in B cell stimulants, which work in autoimmune diseases, such as SLE.(8,19,20) BAFF, especially expressed by monocytes, macrophages, T cells, myeloid cells, and dendritic cells, is activated and in the form of membrane-bound or released as a soluble form and can be measured in plasma.(19,21) BAFF functions as B cell homeostasis, which maintains survival, and in the process of maturation and development of B cells. BAFF functions with the help of A proliferation-inducing ligand (APRIL), which plays a role in regulating the function of B cells. Both type II transmembrane proteins are proteolytically cleaved at the furin protease site and then released as a soluble protein that stimulates humoral effectors.(8,19) An increasing BAFF level in patients can result in disease severity and pathogenic autoantibody. In the beginning, the function of BAFF was to stimulate B cell proliferation and cytokine production, as well as to induce immunoglobulin. Excessive B cell activation in SLE patients contributes to the increasing level of BAFF, leading to the regulation of BAFF expression.(8,22) BAFF plays a significant role in the treatment of autoimmune diseases or cancer.(19) BAFF will bind with three receptors expressed by transmembrane and calcium modulator and cyclophilin ligand interactor (TACI), B cell maturation

**Table 1. Effectiveness of therapy in SLE patients.**

| Drugs | Efficacy and Safety of Therapy | References |
|---|---|---|
| Belimumab | - Improvements in the majority of SRI-4 response rate, SELENA-SLEDAI (≥4-point reduction) and BILAG organ system<br>- Improvement of clinical laboratory data such as hematology, liver function, electrolytes, and urin alysis<br>- Primary efficacy renal response/renal improvements<br>- Lower risk of severe flares, measured by SFI in SLE patients<br>- Reduce SLE disease activity of patients<br>- Reduce corticosteroid dose by ≥25% (previously >7.5 mg/day to ≤7.5 mg/day) | (21,30,34,35,38,60–64) |
| Belimumab + Rituximab + Cyclophosphamide | - Reduction in SLEDAI of (≥4-point) and no worsening of PGA score of >0.3 points on a scale of 0-3<br>- Reducing the dose of steroid drugs to ≤5 mg/day<br>- Response renal with proteinuria <0.75 gr/24 hours and serum creatinine within 125% of baseline<br>- No activity in major organ systems such as gastrointestinal, hemolytic anemia<br>- Feasibility and safety of adverse events to infection (monitoring is required)<br>- Reduction of anti-dsDNA and sustained B cell depletion | (37,41) |
| Blisibimod | - There were no changes in the clinical conditions measured such as the electrocardiography and the patient's vital signs of SLE patients<br>- Decreased B cell<br>- Reduced disease activity and prevent disease severity<br>- Primary efficacy of SRI-4 at from week 16 week<br>- Reducing the dose of Prednisone drugs to ≤7.5 mg/day at form<br>- Achieved >50% reduction in UPCR from baseline<br>- Modest improvements in the Lupus QoL total score | (18,44) |
| Rituximab | - CRR and PRR to 66%, renal improvement | (40) |
| Tacrolimus | - Reduction in renal flares | (51) |
| Tacrolimus compared to Cyclophosphamide | - Reducing urine protein levels by administering Tacrolimus compared to administering Cyclophosphamide<br>- Increased serum albumin levels by administering Tacrolimus compared to administering Cyclophosphamide<br>- Decrease SLEDAI score by administering Tacrolimus compared to administering Cyclophosphamide<br>- Increase complete remission<br>- Anti dsDNA negative conversion rate<br>- Gastrointestinal symptoms and irregular menstruation less frequent in patient treated with Tacrolimus | (65) |
| Mycophenolate Mofetil compared to Cyclophosphamide | - Mycophenolate Mofetil and Cyclophosphamide are effective in inducing remission through decreasing proteinuria and improving renal function<br>- Mycophenolate Mofetil treatment showed a better safety profile with fewer adverse events compared to Cyclophosphamide | (43,66,67) |
| Dapirolizumab Pegol | - No side effects were reported, no thromboembolism or death<br>- BILAG assessment is 46% (4 of 11 patients)<br>- SRI-4 responded by week 12 | (32) |
| RSLV-132 | - Decrease in SLEDAI score, but placebo had an improvement in SLEDAI score | (57) |
| Tabalumab | - Safe effect on renal<br>- There was no change in flare since the start of administration<br>- There was no different in serum creatinine concentration, glomerular filtration rate and urine protein/creatinine ratio<br>- SRI-5 in response rates over the 52-week treatment | (45–47) |
| Epratuzumab | - Included BILAG improvement without worsening<br>- Included SLEDAI-2K-6 and decrease from baseline to week 108<br>- PGA score improved significantly from baseline to the last visit | (68) |
| Rontalizumab | - Efficacy response rates by BILAG and SRI sere similar between Rontalizumab and placebo<br>- SRI response was higher<br>- Low dose of steroid in the Rontalizumab treated patient | (56) |
| Sirukumab | - Reduction in SELENA-SLEDAI score (4)<br>- Reduction in BILAG-3<br>- Reduction in PGA-0.7<br>- Mean concentration of C-reactive protein, serum amyloid and vascular endothelial growth factor decreased by week 1-14 | (52) |
| Ocrelizumab | - Renal response was 66.9% at 48 weeks<br>- The most common adverse effect was diarrhea, upper respiratory tract infection, infusion-related reaction and nasopharyngitis with a low percentage | (53) |

antigen (BCMA), and BAFF-R, which was expressed by B cell on maturation and differentiation. BAFF binds to its receptors with different affinity, with BAFF-R being the strongest, followed by TACI and BCMA. BAFF signaling works by binding to BAFF-R through two pathways: NF-κB and phosphatidylinositol-3 kinase (PI3K). APRIL is also a molecule that functions together with BAFF and will bind with BCMA and TACI receptors through the NF-κB pathway.(8) Therefore, BAFF can be used as the targeted therapy for autoimmune diseases, such as SLE, through direct inhibition of its receptors, such as BAFF-R, TACI, and BCMA.(23) The inhibition of the receptor action can prevent further activation of the B cell mechanism in producing the antibody (Figure 2).

Therapy targeting the B cell and cytokine is an important achievement in SLE treatment. In a phase III clinical trial, it was discovered that the level of BAFF at a rate of 2 ng/mL might become a screening parameter and an independent prognostic factor for the increasing phenomena of moderate to severe lupus flare. Several studies have reported a correlation between the level of BAFF serum and measurements of SLE disease activity, such as the safety in lupus national assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score and Mexican Systemic Lupus Erythematosus Disease Activity (Mex-SLEDAI).(8)

**A20 Enzyme: The Function and Association with SLE**

The A20 enzyme is a ubiquitin-modifying enzyme that acts through NF-κB signaling and TNF-mediated apoptosis.(24) A20 protein consists of the N-terminal ovarium tumor (OTU) domain, followed by seven domain zinc finer, as well as 790 residues of the amino acid. NF-κB hyperactivity and nucleotide-binding domain-like receptor (NLRP3) activation impact the excessive production of inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-18, and TNF-α. A20 acts as an enzyme, which has the function of erasing the ubiquitin chain that is linked to K63 through the OTU (deubiquitination) domain, attaching the ubiquitin chain to K48 (ubiquitination), and acting after the translational to regulate the cell function.(25,26)

A20 expression is controlled by NF-κkB, which can lead to inflammation of multiple organs and death. A20 deficiency can disrupt immunity homeostasis, inflammation, cell proliferation, energy products, oxidoreductase activity, lipid metabolism, and fatty acid. The promoter analysis identified several transcription factors involving NF-κB function. The T cell and B cell regulatory functions of A20 could be classified as innate cell regulation.(26,27) Disruption of A20 regulation in myeloid cells can lead to increased signaling of NF-kB as a negative regulator of gene expression and proinflammatory in SLE.(28)

**Inhibitor of BAFF and A20 Enzyme in SLE Treatment**

The use of single therapy and combination with standard therapy in SLE patients or with dose comparisons shows the effectiveness and safety profile of side effects (Table 1). Therapies targeting proteins involved in SLE pathogenesis such as BAFF and A20 enzymes have been reported in previous studies (Table 2).

***Belimumab***

Belimumab is a monoclonal antibody therapy used in combination with standard treatment for SLE patients. Belimumab is a monoclonal antibody therapy used in combination with standard treatment for SLE patients.(22,29) Belimumab neutralizes the factor of B cell survival, which acts by binding the soluble BAFF, and prevents it from binding with its receptors, including BAFF-R, TACI, and BCMA. Therefore, it reduces the number of active peripheral B cells. A clinical trial reported on the safety and tolerance of Belimumab, which showed the presence of reducing B cells when compared with a placebo.(29,30) Therapy with Belimumab gave a good response rate in SLE Responder Index (SRI), SELENA-SLEDAI, British Isles Lupus Assessment Group (BILAG) organ system and renal improvements in SLE patient, furthermore reduce corticosteroid dose by ≥25% (previously >7.5 mg/day to ≤7.5 mg/day), lower risk of severe flares it measured by SELENA-SLEDAI Flare Index (SFI) in SLE patients. Belimumab can be well-tolerated, and there are no significant differences in side effect frequency between the Belimumab and placebo groups. Ten mg/kg dosage of Belimumab was approved by U.S. Food and Drug Administration in 2011 as an additional therapy for SLE patients.(31–33)

Belimumab has a greater therapeutic benefit than standard therapy alone in patients with higher disease activity, anti-dsDNA positive, and receiving corticosteroid treatment as standard therapy in SLE. In a phase III clinical trial conducted using a randomized, double-blind population, which was divided into two groups, the first group received Belimumab while the other group received placebo and continued to receive standard therapy. A 10 mg/kg body weight dosage was given for 104 weeks, resulting in the group who received Belimumab and standard therapy significantly having a primary efficacy response on kidneys compared with the group who received only standard therapy. In SLE patients with lupus nephritis, there is an

**Table 2. Therapeutic targets of BAFF Protein and Enzyme A20 in patient with SLE.**(continue)

| Therapy | Mechanism Action | Methods | Population | Subject | Conclusion | References |
|---|---|---|---|---|---|---|
| Belimumab | Inhibits B- cell activating factor (BAFF) | RCT (ClinicalTrials.gov identifier: NCT01639339) | United States, Belgium, Argentina, the Netherlands, and Italy | 448 patients (224 patients: Belimumab + standard therapy; 224 patients: placebo) | Belimumab administration with standard therapy gave significant primary efficacy renal response compared to placebo. | (30) |
| Belimumab + Rituximab + Cyclophosphamide | Targeting BAFF and suppressing the immune response | RCT (ClinicalTrials.gov identifier: NCT02260934) | United States | 43 patients (22 patients: Rituximab + Cyclophosphamide; 21 patients: Rituximab + Cyclophosphamide + Belimumab IV) | Belimumab and Rituximab combination therapy is safety for SLE patients with comorbid Lupus Nephritis. | (37) |
| Belimumab | Inhibits BAFF | RCT (ClinicalTrials.gov identifier: NCT01649765) | North America, Central America and South America, Europe and Japan | 93 patients (40 patients: placebo; 53 patients: Belimumab IV) | Belimumab has been shown to be effective on renal function at a dose of 10 mg/kg IV and provides the same pharmacokinetic benefits as belimumab in adults and children. | (38) |
| Belimumab | Inhibits BAFF | RCT (ClinicalTrials.gov identifier: NCT01345253) | Japan | 60 patients (39 patients: Belimumab; 21 patients: placebo) | Organ system improvements were seen in more Japanese patients treated with Belimumab than in patients receiving placebo. | (34) |
| Belimumab + Rituximab | Inhibits BAFF and B cell reduction | RCT (ClinicalTrials.gov identifier: ISRCTN47873) | English | 56 patients (28 patients: Belimumab + Rituximab; 28 patients: placebo after Rituximab) | Belimumab combination therapy followed by Rituximab may be an option in patients with active SLE. | (41) |
| Belimumab | Inhibits BAFF | RCT (GSK Study: BEL112341; NCT01484496) | North America, Central America, South America, West Europe, Eastern Europe and Asia | 662 patients (456 patients: Belimumab; 206 patients: placebo) | Belimumab SC can be used as an adjunct therapy for 24 weeks. | (33) |
| Belimumab | Inhibits BAFF | RCT (GSK Study: BEL113750; ClinicalTrials.gov identifier: NCT01345253) | Japanese | 60 patients (39 patients: Belimumab; 21 patients: placebo) | Belimumab has such efficacy as an adjunct therapy option for the Japanese population of SLE patients. | (61) |
| Belimumab | Inhibits BAFF | RCT (BLISS-52: NCT00424476; BLISS -76: NCT00410384; BLISS-SC: NCT01484496; North-East Asia study-IV: NCT01597622) | Latin America, Asia Pacific and Eastern Europe, Northeast Asia (China, Japan and South Korea) and Australia | 1375 patients (597 patients: Belimumab IV; 248 patients: Belimumab SC; 530 patients: placebo) | Belimumab IV and SC therapy showed an efficacious effect in SLE patients compared to placebo. | (35) |
| Belimumab | Inhibits BAFF | RCT (GSK Study: BEL112341; ClinicalTrials.gov identifier: NCT01484496) | US, Americas excluding US Western Europe/Australia/Israel Eastern Europe, Asia | 356 patients (248 patients: Belimumab; 108 patients: placebo) | Administration of Belimumab SC 200 mg can significantly improve response to therapy and reduce severe flares and help reduce corticosteroid use when compared to placebo. | (60) |
| Belimumab | Inhibits BAFF | RCT (GSK Study: BEL113750; ClinicalTrials.gov identifier NCT01345253) | China, Japan and South Korea | 677 patients (451 patients: Belimumab; 226 patients: placebo) | Belimumab is effective in the treatment of SLE and may reduce the use of prednisone. | (62) |
| Belimumab | Inhibits BAFF | RCT (Systematic Review) | North/Central/south America, Western Europe, Australia, Asia, USA, Canada | 5 articles (3460 patient) included through MEDLINE, EMBASE, and the Cochrane | The administration of Belimumab at doses of 1 and 10 mg/kg IV and belimumab 200 mg SC when combined with standard therapy has shown an efficacious effect and there are no reports of a significant risk of side effects. | (21) |
| Belimumab | Inhibits BAFF | RCT (ClinicalTrials.gov identifier: NCT01484496) | North, Central, and South America, Eastern and Western Europe, Australia, and Asia | 836 patients (556 patients: Belimumab; 280 patients: placebo) | The use of Belimumab SC 200 mg can reduce SLE disease activity and has a good safety profile compared to placebo. | (69) |
| Blisibimod | Inhibits BAFF | RCT (Clinicaltrials.gov identifier: NCT02411136) | Asian and Pacific Islander | 54 patients (40 patients: Blisibimod; 14 patients: placebo) | The use of Blisibimod was well tolerated and the safety profile was the same as that of placebo. | (44) |

(continue) **Table 2. Therapeutic targets of BAFF Protein and Enzyme A20 in patient with SLE.**

| Therapy | Mechanism Action | Methods | Population | Subject | Conclusion | References |
|---|---|---|---|---|---|---|
| Belimumab | Inhibits BAFF | RCT (ClinicalTrials.gov identifier: NCT00410384) | Asian, African American | 1125 patients (563 patients: Belimumab + standard therapy; 562 patients: placebo) | Belimumab can be used as an adjunct therapy in SLE patients and in combination with standard therapy. | (63) |
| Belimumab | Inhibits BAFF | RCT (ClinicalTrials.gov identifier: NCT00071487; NCT00583362) | Caucasian, African American, Asian and others | 449 patients (336 patients: Belimumab; 113 patients: placebo) | Belimumab plus standard therapy has been shown to be well tolerated in a city of 4 years and Belimumab in long-term. | (64) |
| Rituximab | Rituximab (anti CD20) targets B cell reduction | Systematic Review (24 prospective studies, 3 randomized controlled trials dan 4 retrospective studies) | Caucasian, Hispanic, African, America, East Asian, and Indian | 31 studies in the treatment group received Rituximab, Belimumab, Steroids Cyclophosphamide, and Mycophenolate mofetil | Administration of Rituximab and cyclophosphamide is superior to administration of cyclophosphamide and provides a safe renal profile. | (40) |
| Tacrolimus | Monoclonal antibodies as anti-CD20 and calcineurin inhibitor | RCT (ClinicalTrials.gov identifier: NCT00371319) | Hongkong | 150 patients (76 patients: Mycophenolate mofetil; 74 patients: Tacrolimus) | Tacrolimus is safe for the kidneys with a lower eGFR value than Mycophenolate mofetil. | (51) |
| Blisibimod | Inhibits BAFF | RCT (ClinicalTrials.gov identifier: NCT01395745) | Belarus, Brazil, Colombia, Georgia, Guatemala, Hong Kong, Korea, Singapore, Malaysia, Mexico, Russia, Sri Lanka, Taiwan, Thailand and the Philippines | 442 patients (245 patients: Blisibimod; 197 patients: placebo) | The use of Blisibimod can help reduce steroid use, decrease proteinuria and response to biomarkers such as B cells. | (18) |
| Dapirolizumab pegol | Anti-CD40 ligan | RCT (article) | Europe | 24 patients (16 patients: Dapirolizumab pegol; 8 patients: placebo) | Dapirolizumab may be an effective treatment in SLE but further safety and efficacy testing is needed. | (32) |
| RSLV-132 | Digests RNA bound to autoantibodies enzymatically | RCT (ClinicalTrials.gov identifier: NCT02194400) | United States | 32 patients (24 patients: RSLV-132; 8 patients: placebo) | RSLV is safe to use for SLE patients. | (57) |
| Tabalumab | Dissolving BAFF | RCT (ClinicalTrials.gov identifier: NCT01205438; NCT01196091) | Black/African American | 2262 patients SLE | Tabalumab had no significant effect on creatinine concentration, glomerular filtration rate, protein ratio. | (45) |
| Tabalumab | Dissolving BAFF | Phase I Clinical Studies | Caucasian, Hispanic dan others | 23 patients (17 patients: Tabalumab; 6 patients: placebo) | Administration of a single dose of Tabalumab given IV or SC shows good tolerance. | (46) |
| Epratuzumab | Binds to CD22 as a co receptor of B cell | RCT (ClinicalTrials.gov identifier: NCT00111306; NCT00383214) | Ethnic White, black, Asian and others | 227 patients (39 patients: 200 mg Epratuzumab; 38 patients: 800 mg Epratuzumab; 37 patients: 2400 mg Epratuzumab; 38 patients: 3600 mg Epratuzumab) | Epratuzumab a treatment is well tolerated with long-term use. | (68) |
| Tabalumab | Dissolving BAFF | RCT (ClinicalTrials.gov identifier: NCT01205438) | Asian, Black/African-American, Hispanic/Latin, and others | 1124 patients (372 patients: Tabalumab every 2 weeks; 376 patients: Tabalumab every 4 weeks; 376 patients: placebo) | The use of Tabalumab has similar safety to placebo. Side effects reported as patients tend to feel depressed. | (47) |
| Rontalizumab | Anti IFN alpha and prevents signaling via type I IFN receptors | RCT (ClinicalTrials.gov identifier: NCT00962832) | Ras white, American Indian, Africa American and Asian | 238 patients (159 patients: Rontalizumab; 79 patients: placebo) | Rontalizumab is safe and well tolerated in active lupus patients. | (56) |
| Sirukumab | Anti–IL-6 monoclonal antibody that binds to IL-6 | RCT (ClinicalTrials.gov identifier: NCT01702740) | Caucasian and Asian | 238 patients | Sirukumab is well tolerated at a dose of 10 mg/kg every 2 wk. There have been reports of side effects, such as an increase in total cholesterol in the blood. | (52) |
| Ocrelizumab | Monoclonal antibody which selectively targets and depletes CD20 B cells in peripheral circulation | RCT (ClinicalTrials.gov identifier: NCT00626197) | White, Asian, American, Indian/Native Alaskan Black and others | 381 patients (126 patients: placebo; 127 patients: Ocrelizumab 400 mg; 128 patients: Ocrelizumab 1000 mg) | Ocrelizumab had no beneficial effect in this study and should therefore be discontinued early. | (53) |

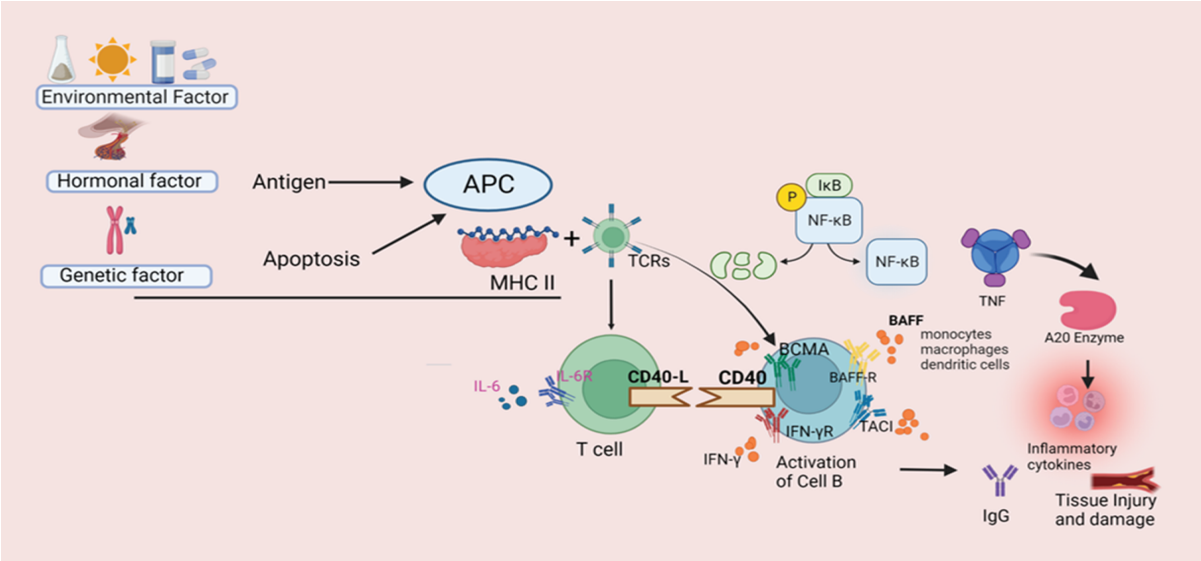


**Figure 2. Signaling pathway of T cell and B Cell of SLE.**

increased level of BAFF in the kidney and serum; therefore, a blocking agent is required to inhibit BAFF by reducing B cell function and regulation, reducing the production of an antibody, and inhibiting the formation of lymphoid structures inside the kidney. Belimumab is a recombinant IgG monoclonal antibody therapy, which acts through the inhibition of BAFF. It was reported that patients receiving Belimumab showed less impaired renal function with decreased proteinuria.(21,30,34,35)

The effectiveness of combination therapy of Belimumab with Rituximab as an anti-CD20 targeting B cell reduction and BAFF inhibitor was done in 43 SLE patients from the United States population of ethnicity is White, Black, Asian, Hispanic, or Latino as well as 56 subjects from the Britain population. The dose can be administered intravenously (IV) at 10 mg/kg, which has been shown to be effective on renal function and to have similar pharmacokinetic effects in child and adult patients. Belimumab can also be administered in conjunction with standard therapy to SLE patients. The study in a population of White/Caucasian, Asian, and African Americans, as many as 1125 subjects, where 563 subjects received Belimumab at 10 mg/kg with standard therapy (steroids), while 562 subjects received placebo with standard therapy revealed that both can be used as an effective combination therapy in SLE patients.(36,37) Ninety-three patients, 40 of whom received a placebo and the other 53 who received Belimumab, had pharmacokinetic results that were safe and effective as adults taking Belimumab.(38) Adverse effect of using Belimumab have been reported such us infections arthralgia, headache, rash, diarrhea and nausea, urticaria, chest pain as infusion reaction. Hematologic reaction such as neutropenia and thrombocytopenia have also been reported. The use of Belimumab during pregnancy, breastfeeding, the elderly and children has not been reported, so caution should be exercised in its use. In clinical studies, the incidence of psychiatric disorders was higher in patients who received Belimumab than placebo (0.8% *vs.* 0.4%). Furthermore, the use of Belimumab together with Cyclophosphamide should be avoided because it is associated with kidney and central nervous system disorders.(39)

***Rituximab***

Rituximab is a monoclonal antibody that has the function of binding CD20 on the surface of B cells and A20 enzymes controls signals induced by B cell receptors, including through the NF-κB pathway. By binding to CD20, Rituximab induces depletion of B cells, leading to a decrease in the number of circulating B cells. This depletion of B cells is thought to be the main mechanism of action of Rituximab. Rituximab treatment has been shown to increase BAFF levels during B-cell depletion. This increase in BAFF levels may be a compensatory response to the depletion of B cells. However, upon B-cell repopulation, BAFF levels decline and return close to pre-treatment levels.(36)

The advantage of Rituximab + Cyclophosphamide over Cyclophosphamide alone is 64% *vs.* 21% complete renal response (CRR) and 19% *vs.* 36% partial renal response (PRR). Six prospective and retrospective studies, which used Rituximab monotherapy, discovered 66% CRR or PRR in all the patients. Eleven studies, which examined Rituximab combined with Cyclophosphamide

or Mycophenolate mofetil also discovered 66% CRR or PRR in all the patients. The CRR rate for patients are Caucasian (77%), East Asian (38%), and Hispanic (28%). (40) Rituximab treatment has been proven to give a response on SLE patients by depleting B lymphocytes. On a subset of SLE patients with high-level anti-dsDNA antibody, clinical relapse occurred in lower B cell counts after treatment compared with before Rituximab treatment and was associated with a higher proportion of plasma blast repopulation in peripheral blood. Belimumab combination therapy followed by Rituximab may be an option in patients with active SLE.(41) Reports of side effects of using Rituximab have not been widely reported. A retrospective study of 136 SLE patients, namely looking at adverse reactions to Rituximab infusion, states that there is an effect of back pain experienced by patients.(42)

***Cyclophosphamide***

Cyclophosphamide was known as a B cell and T cell inhibitor, it also modulated T cell response and B cell antibody production. In a phase II clinical trial carried out in the United States population, the participants received 100 mg Methylprednisolone, 1.000 mg Rituximab, and 750 mg Cyclophosphamide IV for 2 weeks straight. It was followed by maintenance therapy of 40 mg/day Prednisolone for 96 weeks. In the fourth week, patients were divided into two groups: group I received Rituximab and Cyclophosphamide, as well as a Belimumab IV infusion, with a 10 mg/kg dosage on the fourth, sixth, and eighth week, followed by every four weeks until week 48. On the other hand, group 2 received only Rituximab and Cyclophosphamide (RC). Urine protein creatinine ratio (UPCR), estimated glomerular filtration rate (eGFR), and serum albumin level tests indicated the same value for both groups. High dose administration is effective in inducing remission with reduced renal relapse and decline percentage positivity of anti-dsDNA antibody was 29–44%. Decrease of SLEDAI score shown by patients. B cell reduction can be seen in both groups in the 12$^{th}$ week with a geometric mean number of B cells, 3 cells/μL (95% CI: 1–10) in the RC group *vs.* 2 cells/μL (95% CI: 1–3) in the Rituximab + Cyclophosphamide + Belimumab (RCB) group. Next, the number of B cells was consistently lower in the RCB group. The differences were still significant on week 60, 12 weeks after belimumab treatment was stopped with a geometric mean number of B cells, 53 cells/μL (95% CI: 26–109) in the RC group *vs.* 11 cells/μL (95% CI: 6–20) in the RCB group ($p$=0.0012). Belimumab combination therapy with Rituximab could be considered safer for patients with lupus nephritis in SLE patients as it can reduce the maturation of B cell transition and increase the negative selection of autoreactive B cells.(37) Comparison of the effectiveness of low dose IV Cyclophosphamide and oral Mycophenolate mofetil, namely that they are equally effective in terms of efficacy and safety for patients with less severe lupus nephritis. Likewise, there are reports of side effects of low dose IV Cyclophosphamide on the gastrointestinal and safer renal responses.(43)

***Blisibimod***

Blisibimod is the strongest and most selective BAFF inhibitor on autoimmune diseases.(18,44) A phase III clinical trial of 442 SLE patients evaluated the effectiveness and safety of Blisibimod. It was a randomized, double-blinded, and placebo-controlled trial. Analysis results from this study identified greater treatment effects on the patients admitted with the highest activity, administration of a higher dose of Corticosteroid, anti-dsDNA, and low complement C3 or C4. Patients who received weekly subcutaneous 200 mg Blisibimod showed improvement in disease activity assessment index using SELENA-SLEDAI, which was previously ≥10. There was a reduced dosage of corticosteroid in the eighth week. In the 52$^{nd}$ week, the assessment showed the respondent index to be 6. Statistical analysis revealed that subjects treated with Blisibimod significantly achieved a reduction of corticosteroids. There was also a reduction of SLE and B cell autoantibody, as well as an increased complement of C3 and C4. Blisibimod can be well-tolerated even though it has side effects, such as upper respiratory tract infection, urinary tract infection, erythema, and diarrhea.(18) Blisibimod treatment is associated with a significant reduction in anti-dsDNA, immunoglobulin, total B cell number, and significantly increased complement of C3 and C4, and its usage can help reduce Corticosteroid usage.(39)

***Tabalumab***

Tabalumab is the most recent BAFF antagonist under clinical evaluation. Tabalumab binds the BAFF which can be dissolved in the membrane but not in APRIL, as we know that cytokines that are important for B cell development and function. Therefore, the Tabalumab did not undergo the phase 1 or 2 evaluation in SLE, but it went straight to two separate studies of phase 3 in SLE.(45)

Tabalumab was administered subcutaneously. Therefore, it has the same benefits as Blisibimod in maintaining control of circulating drug levels in blood. Furthermore, Tabalumab may be more immunogenic than Blisibimod because it is not a synthetic agent. However,

it was difficult to imagine how Tabalumab was superior to Belimumab (which was also not synthetic), except the neutralization of BAFF membrane added additional therapeutic benefit beyond that achieved by neutralization of dissolved BAFF alone.(46) The therapy is administered in the induction phase by giving glucocorticoid in combination with an immunosuppressive agent, such as Cyclophosphamide or Mycophenolate Mofetil, to suppress kidney inflammation and maintain immunity. Next, maintenance therapy was administered to prevent renal attacks, minimizing glucocorticoid exposure and toxicity from immunosuppressive agents.(47) There may be adverse effects from using Tabalumab, the risk of depression and suicidal ideation that often occur. Side effects of using Tabalumab were also reported to be changes in serum creatinine concentration and eGFR. Tabalumab also directly affects kidney disorders and flares in lupus nephritis.(48)

***Tacrolimus***

A randomized control trial research showed that the use of multi-targets, such as Mycophenolate mofetil and Tacrolimus, was more effective than just Cyclophosphamide IV. Tacrolimus is an immunosuppressive agent that inhibits T cell-specific calcineurin, while Mycophenolate mofetil functions by inhibiting the proliferation of B and T cells. (49,50) BAFF and the A20 enzyme are regulators that influence the function and interaction of T cells and B cells. Tacrolimus is used as a therapy in SLE patients in combination with high dose Prednisolone. Compared with Mycophenolate mofetil, Tacrolimus therapy as induction therapy gave a good renal response with creatinine ≤0.75 and eGFR 80 mL/min on the 18$^{th}$ month. Predicting 10 year outcomes that are suitable targets for induction therapy yields the best results.(51)

The adverse effect of using Tacrolimus was reported that there was a lower tendency to die than the control group, although it was not significant. Likewise with the incidence of infection and liver dysfunction. However, what is of concern is the reduction in leukopenia, gastrointestinal disturbances, menstrual cycles, hypertension and hyperglychemia in the Tacrolimus group.(49,50)

***Sirukumab***

Sirukumab is an monoclonal antibody therapy that function induced B cell differentiation by inhibiting the production of IL-6 cytokines. IL-6 induces B cell differentiation to form antibodies, such as antinuclear antibodies, anti-dsDNA, immune complex, and inflammation in tissues and organs. Interleukin 6 can increase the activity of NF-κB while A20 can suppress the activity of NF-κB and inflammation. By binding IL-6, inflammatory events can be controlled. A study conducted in the Caucasian and Asian population involving 238 subjects concluded that Sirukumab was well-tolerated at a dose of 10 mg/kg every two weeks. Reduction in SELENA-SLEDAI score, BILAG-3 and Physician Global Assessment (PGA)-0.7 indicated by the patient's response after therapy.(6) Mean concentration of C-reactive protein, serum amyloid and vascular endothelial growth factor decreased by week 1–14. However, there have been reports of side effects, such as an increase in total blood cholesterol. The use of Sirukumab can be tolerated in SLE patients at a dose of 1–10 mg/kg every 2 weeks. But need to be monitored for a decrease in the number of neutrophils, white blood cells and platelets.(52) Research using this drug is still rarely reported.

***Ocrelizumab***

Ocrelizumab therapy is a monoclonal antibody that has selective targets and depletes CD20 on B cells. The BAFF protein influences the function and interaction between T cells and B cells. While the A20 enzyme inhibits excessive activation, and BAFF regulates the survival and function of B cells. The RCT study, in white population, Asian, American, Indian/Native Alaskan, Black, and other population involving 381 subjects, it was discovered that this drug did not provide a beneficial effect and required the study to be discontinued.(53) Renal response was 66,9% at 48 weeks. Studies of the potential role of Ocrelizumab in SLE patients reported no MRI activity and no problems in a phase II double blind study such as infection, leukoencephalopathy but one death was reported at high doses of ocrelizumab and also respiratory and urinary tract infections.(54) Research using this drug is still rarely reported.

***Rontalizumab***

SLE treatment focuses on the molecular targets involved, including TNF members such as BAFF, cytokines secreted from immune cells such as interleukins, cell antigens such as CD20 and CD22 and IFN-α.(55) Rontalizumab is an anti-IFN-α therapy and prevents signaling through type I IFN receptors. The elevated IFN-α serum levels in SLE patients are associated with flare and disease activity. A research study conducted on 238 subjects from the White, American Indian, African American, and Asian population discovered that active SLE cases, compared with placebo rontalizumab, were well-tolerated, with reduced disease progression.(56) Clinical outcomes show response rates by BILAG and SRI sere similar between Rontalizumab and placebo and

low dose of steroid in therapy of patient. A double blind phase I study to look at the safety and pharmacodynamics of Rontalizumab in SLE patients showed that there was an imbalance between side effects in patients who received therapy and those who received placebo, such as grade III side effects for the infection category (sinusitis and bronchitis), urinary tract infections, and a serious infection namely appendicitis was reported.(55)

***RSLV-132***

The phenomenon of SLE is associated with an apoptotic process that triggers a loss of self-tolerance and the development of autoantibodies. Recognition of autoantibodies then transmitted the RNA to the intracellular compartment of immune cells and activated toll-like receptors, may trigger proinflammatory cytokines. By administering RSLV-132, it is possible to digest RNA bound to autoantibodies without activating the inflammatory pathway by involving enzymes. A study conducted on the United States population concluded that this drug is safe to be given to SLE patients. Additionally, RSLV-132 can affect SLE biomarkers, such as IFN-α, which neutralizes cytokines. BAFF is a protein induced by IFN-α, which shows a decrease in serum BAFF levels in the group receiving RSLV-132 compared with placebo. Condition of patients showed improvement in the SLEDAI score. Intravenous infusion of RSLV-132 has been shown to be safe and tolerable in SLE patients and adverse effects such as headache, urinary tract infection, vomiting, upset stomach and dizziness were all grade I and have not been shown to be associated with this drug. And also not reported any death status.(57) Research using this drug is still rarely reported.

***Epratuzumab***

One of the drugs used for SLE patients is Epratuzumab, a B cell modulator. This drug functions by binding the CD22, a B cell co-receptor; therefore, it can modulate B cell activity. CD22 can also regulate the regulator balance of IL-10 and proinflammatory cytokines through elevated IL-10 expression and the inhibition of proinflammatory cytokines IL-6 and TNF.(58)

The clinical outcomes reported are BILAG and SLEDAI-2K-6 score improvement without worsening and decrease from baseline to week 108. PGA score improved significantly from baseline to the last visit. The most common side effects found in the use of this drug are headaches, nausea, dizziness and upper respiratory tract infections.(31) Research using this drug is still rarely reported.

***Dapirolizumab pegol***

SLE patients are associated with the interaction of CD40 and CD40 ligands, which activate B cells and the antigenic percentage of cells and platelets. CD40 ligands are expressed by $CD4^+$ T cells and thrombosis.(59) However, CD40 is expressed by antigen-presenting cells and B cells; therefore, their interaction can be an important modulator of immune inflammation in SLE. A20 can limit NF-κB signaling at the CD40 receptor. Functional interactions between T cells and normal B cells induce dendritic cell maturation. One of the drugs used to block CD40 ligands is Dapirolizumab pegol. Clinical outcomes of using Dapirolizumab pegol improvement of BILAG assessment is 46% and SRI-4 responded by week 12. No side effects were reported, no thromboembolism or death.(32)

Numerous studies have been conducted on BAFF protein-based SLE therapy, which is considered an effective treatment for SLE patients but has not been fully utilized the mechanism of action of this therapy is not fully understood. Thus, it is difficult to know treatment can increase disease activity and improve patient quality of life. It is necessary to conduct clinical trials in all populations of SLE patients.

**Future Promising Therapeutic Target**

In this search, not many clinical trial studies have been found to determine A20 enzyme is used as a therapeutic target. However, it needs to be considered as a therapeutic target given its role in NF-κB pathway. A better understanding of the regulation of A20, its molecular targets, and its role in SLE patients is required. A20 can be promising as a therapeutic target in several autoimmune and inflammatory diseases such as SLE. The discovery of new drugs in SLE treatments is promising in the management of SLE, but more in-depth clinical research into the involvement of SLE comorbidities is required. From the results of this search, it can be concluded that BAFF and the A20 enzyme can be used as therapeutic targets with a single use or combined with standard therapy in patients with SLE, as well as the safety of side effects in patients with SLE, but it is necessary to understand the mechanism of the specific pathway and develop better therapies. So far, utilizing a single therapy that targets proteins directly involved in the pathogenesis of SLE has proven to be more effective than just receiving standard therapy. Several studies have highlighted the efficacy and safety of this approach, including kidney safety, reducing flares, preventing disease severity, and lowering corticosteroid doses. Additionally, combining monoclonal antibody therapy with immunosuppressant

agents has shown improvements in SLEDAI scores and no major activity in several organs.

## Conclusion

Study of the effectiveness of therapy in autoimmune diseases, namely by protein targeting. BAFF and A20 enzymes can be used as therapeutic targeted for several autoimmune diseases, such as SLE. Therapy can be administered as a single therapy or in combination with standard therapy in SLE patients, and safety and mild side effects have been reported in SLE therapy. However, it is critical to understand the specific pathway mechanisms for better therapeutic development.

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## Authors Contribution

DRF and MIB were involved in the conceptualization of the manuscript. DRF prepared the draft of original manuscript. TR, LH and MIB were involved in the reviewing and editing process. All authors read and approved the final manuscript.

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