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Clinical Pharmacokinetics and Pharmacodynamics of Biologic Therapeutics for Treatment of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease with potentially severe clinical manifestation that mainly affects women of childbearing age. Patients who do not respond to standard-of-care therapies, such as corticosteroids and immunosuppressants, require biologic therapeutics that specifically target a single or multiple SLE pathogenesis pathways. This review summarizes the clinical pharmacokinetic and pharmacodynamic characteristics of biologic agents that are approved, used off-label, or in the active pipeline of drug development for SLE patients. Depending on the type of target, the interacting biologics may exhibit linear (non-specific) or nonlinear (target-mediated) disposition profiles, with terminal half-lives varying from approximately 1 week to 1 month. Biologics given by subcutaneous administration, which offers dosing flexibility over intravenous administration, demonstrated a relatively slow absorption with a time to maximum concentration of approximately 1 day to 2 weeks and a variable bioavailability of 30–82 %. The population pharmacokinetics of monoclonal antibodies were best described by a two-compartment model with central clearance and steady-state volume of distribution ranging from 0.176 to 0.215 L/day and 3.60–5.29 L, respectively. The between-subject variability in pharmacokinetic parameters were moderate (20–79 %) and could be partially explained by body size. The development of linked pharmacokinetic-pharmacodynamic models incorporating SLE disease biomarkers are an attractive strategy for use in dosing regimen simulation and

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Compliance with Ethical Standards

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optimization. The relationship between efficacy/adverse events and biologic concentration should be evaluated to improve clinical trial outcomes, especially for biologics in the advanced phase of drug development. New strategies, such as model-based precision dosing dashboards, could be utilized to incorporate information collected from therapeutic drug monitoring into pharmacokinetic/pharmacodynamic models to enable individualized dosing in real time.

1 Introduction

Systemic lupus erythematosus (SLE) is the most common and serious form of lupus. Approximately 70 % of the 5 million people with lupus worldwide are diagnosed with SLE and nine out of ten are women, predominantly between 15 and 45 years of age [1]. It is a chronic, incurable autoimmune disease generating autoantibodies that can attack any organ system in the body [2]. Conventional therapies, such as corticosteroids and immunosuppressants, are generally effective but are associated with serious adverse effects. Despite the use of the current standard of care, approximately 60 % of lupus patients continue to experience persistent symptoms and severe disease flares, which necessitates therapies with improved safety and efficacy profiles [3]. Novel biologic therapies targeting single or multiple SLE pathogenesis pathways are being developed to meet these medical needs. Biologics are add-on therapies that are mainly reserved for patients with moderate to severe SLE or with a lack of response to conventional treatments.

Immunopathology of SLE represents a multifactorial imbalance of the innate and adaptive immune responses (Fig. 1). The immune system of an SLE patient has limited capacity to clear apoptotic cell fragments, which activate professional antigen-presenting cells (e.g., dendritic and B cells) for processing and self-antigen presentation to T cells [4]. Primed autoreactive T cells stimulate B cells to produce autoantibodies. Autoantibodies may form inflammatory immune complexes with self-antigens, get deposited to various tissues, and induce organ damage by stimulating local inflammation [4]. Therefore, targeting both innate and acquired arms of immune response could be an important goal of SLE therapy.

In clinical practice, SLE is diagnosed according to the 11 criteria developed by the American College of Rheumatology [5]. These criteria define the clinical manifestation of SLE in terms of skin criteria (malar rash, oral ulcers, photosensitivity, and discoid rash), systemic criteria (pleuritis or pericarditis, arthritis, renal disease, or central nervous system involvement), and laboratory criteria (cytopenias, anti-double-stranded DNA [anti-dsDNA] or antiphospholipid, and antinuclear antibodies) [5]. A patient must meet four of these criteria to be diagnosed as having definite SLE. Clinical scores are often used as the primary endpoint of clinical trials in order to quantify the clinical response patients have to the treatment. For example, the SLE Responder Index (SRI-n) [6], a frequently used scoring system in SLE trials, is a composite endpoint in which patients are considered responders if they meet all of the following criteria: (1) n -point reduction in SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index) score [7]; (2) no new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than one new B organ domain score [8]; and (3) no

worsening (<0.3 -point increase) in Physician's Global Assessment (PGA) score compared with baseline.

This review evaluates the pharmacokinetics and pharmacodynamics of currently approved biologics, biologics with off-label use, as well as biologics undergoing active drug development. A search of the PubMed database and google.com was conducted using the search term "systemic lupus erythematosus" and each of the following terms: "biologics", "monoclonal antibody", "recombinant fusion protein", "pharmacokinetics", and "pharmacodynamics" until November 2015. Journal publications and conference proceedings identified using the aforementioned method were reviewed. The current development phases of identified biologics were further verified in the AdisInsight database. A total of eight biologics with available pharmacokinetic/pharmacodynamic information for the treatment of SLE, grouped by their mechanism of action, are included in this review and their clinical pharmacokinetics/pharmacodynamics, pharmacometric modeling, and alternative delivery route information are discussed. The information is presented to support the use of modeling and simulation in order to assist the design of dosing regimens for future trials and to facilitate individualized dosing in SLE patients in clinical practice.

2 Structure of Biologic Therapeutics

The biologics indicated for SLE treatment are largely monoclonal antibodies (belimumab, rituximab, anifrolumab, AMG 557, AMG 811) that are derived from human immunoglobulins (Ig) of the G isotype (IgG) (Table 1). There are four IgG subtypes (IgG1, IgG2, IgG3, and IgG4) in humans, named in order of their abundance in circulation, with IgG1 being the most abundant [9]. All of the monoclonal antibodies summarized in this review are derived from the IgG1 subtype, except AMG 557 (IgG2). IgG is a hydrophilic, large protein molecule (146 kDa) that is composed of two identical antigen-binding regions (Fab) and one crystallizable region (Fc) [10]. The Fc region is important in determining the pharmacokinetic profile of the monoclonal antibody as it binds to neonatal Fc receptor (FcRn), which protects the molecule from intracellular catabolism and prolongs its half-life in systemic circulation [11]. Recombinant fusion proteins, blisibimod and atacicept, are composed of the antigen-binding, extracellular portion of the receptor or polypeptides, fused to a human IgG1 Fc region. This structure maintains a long half-life of at least a week, while it binds to the targets in a dual blockage mode (B lymphocyte stimulator [BLyS, also known as B cell-activating factor (BAFF)] and a proliferation-inducing ligand [APRIL]) or possesses 250-fold higher binding affinity (1 pM) to the target (BLyS) than with belimumab due to the specifically engineered antigen-binding domains [12, 13]. It remains to be seen if any of these anti-BLyS pipeline products could exhibit superior efficacy to belimumab. CDP7657 is a Fab fragment of an anti-cluster of differentiation 40 ligand (CD40L) IgG1 monoclonal antibody. By conjugating to the hydrophilic polyethylene glycol (PEG) moiety, CDP7657 demonstrated reduced thromboembolic toxicity in the in vitro tests compared with another anti-CD40L IgG1 antibody hu5c8, the Fc region of which is thought to induce the onset of thromboembolic events through facilitating the crosslinking of platelets in vivo [14].

3 Absorption, Distribution, Metabolism, and Elimination

The majority of biologics developed for SLE treatment are for intravenous administration, which offers immediate central distribution and less variability in pharmacokinetic profiles between patients (Table 2). Subcutaneous delivery of biologics, such as belimumab, blisibimod, atacicept, and AMG 811, provides dosing flexibility and an alternative for intravenous delivery. Depending on the molecular size of the protein molecule, it is absorbed through body tissue penetration or drained via lymphatic vessels into the systemic circulation, with larger molecular weight leading to a higher percentage of the dose being absorbed via the lymphatic system [15]. Due to the nature of variable absorption pathways, biologics given by subcutaneous administration demonstrate a highly variable absorption profile with a time to maximum concentration ($t_{\max}$) of approximately 1 day to 2 weeks and an absolute bioavailability of 30–82 %. The absorption kinetics from the depot to central compartment were described as a first-order process for AMG 811 and the estimated absorption rate constant was 0.178 day^{-1} , similar to the values obtained from monoclonal antibodies used in other disease types [16].

Due to their large molecular size and hydrophilicity, biologic agents mainly distribute within the extracellular fluid space with limited cellular uptake [17]. For example, CDP7657, the PEG-conjugated (PEGylated) Fab portion of an anti-CD40L IgG1 antibody, has a volume of distribution of 4–9 L in healthy individuals and SLE patients [14], which is similar to the volume of vascular and interstitial fluid in humans. The disposition of monoclonal antibodies has been most frequently described by two-compartment models based on the clinical data [16]. A common interpretation of classical two-compartment models, which identifies the central compartment with the total plasma volume and the peripheral compartment with the interstitial space (or part of it), has been challenged by recent research progress. Inspired by the biphasic characteristics of the plasma concentration–time profile, Fronton et al. [18] investigated different options of grouping all tissues into a central and peripheral compartment (lumping) through minimal physiologically based pharmacokinetic modeling to provide a direct link of the minimal lumped models to classical compartment models. The resulting minimal lumped model has only two compartments, with the central compartment comprised of only plasma and lung or all tissues except for adipose, muscle, gut, bone, and skin. The peripheral compartment contains all of the remaining tissues correspondingly. This approach was in good agreement with the preclinical experimental data [18].

Biologics are mainly subject to intracellular catabolism after endocytosis by the reticuloendothelial system (RES). FcRn, which mainly presents on the cell surface of vascular endothelial cells and reticuloendothelial cells, is responsible for the recycling of biologics with a functional Fc region [11]. FcRn binds to the Fc region of monoclonal antibody or its structure derivative, protects it from degradation in cellular lysosomes, and returns it to the cell surface where the biologic is dissociated from FcRn and re-enters the circulation [11]. CDP7657 does not have an Fc region; it is conjugated to a monovalent PEG moiety, an extended, linear, hydrophilic chain structure, which physically shields it from RES uptake or immunologic recognition.

Biologics may exhibit linear or non-linear pharmacokinetic characteristics in dose-escalating studies, as summarized in Table 2. This is explained by the two elimination pathways involved: non-specific (linear) cellular elimination and specific (non-linear) target-mediated elimination. The mechanism of non-specific cellular elimination involves intracellular catabolism following RES endocytosis and FcRn recycling, as mentioned earlier. This phenomenon tends to be linear as the typical doses of biologics lead to therapeutic concentrations that do not saturate the amount of FcRn on the cell surface. Specific elimination involves the binding of the biologic to its target antigen via the Fab region to form the drug–target complex that gets eliminated. The kinetics of the drug–target complex are described by the target-mediated drug disposition (TMDD) model, where it is influenced by the target amount, target turnover rate, the reversible binding between the drug and the target, and the elimination rate of the complex [19, 20]. The contribution of target-mediated clearance to the overall clearance mainly depends on the target amount. The lack of target-mediated clearance could be due to continuous saturation of target antigens by biologic therapeutics. For example, the TMDD were not found to play a substantial role in belimumab pharmacokinetics, as the median day 360 belimumab serum trough concentration for the 1 mg/kg cohort in the phase III trials was 26.33 nmol/L, which was approximately 1000-fold higher than the median baseline BLyS concentration (51 kDa homotrimer) of 0.02647 nmol/L [21]. It was a similar case for AMG 811, where the estimated AMG 811 steady-state concentrations were at least 100-fold higher than total interferon- γ (IFN- γ) concentrations [22]. When the turnover of the target is not known, the TMDD model could be simplified to a pharmacokinetic model that contains both linear first-order and non-linear Michaelis-Menten clearance processes [23, 24]. In patients with SLE, the terminal half-life of biologics varies from approximately 1 week to 3 months (Table 2).

4 Pharmacokinetics/Pharmacodynamics of Biologics Classified by Their Targeting Pathways

A broad range of biologic agents that selectively target one or more immune system pathways are under investigation in order to offer future choices of safer and more effective treatments for SLE [25]. As summarized in Table 1, most biologic entities that have been approved, are used off-label, or are in advanced clinical development (phase II/III) target the B cell pathway (belimumab, rituximab, blisibimod, atacicept) with the exception of anifrolumab, which is the sole remaining type I IFN pathway-targeting agent in active advanced development. Therapeutic targeting of the T cell pathway is emerging as an alternative strategy for treating SLE as several drug candidates of this category have entered early phase I trial development (AMG 557, AMG 811, CDP7657). Further clinical validation is needed to confirm whether the type I IFN- or T cell-targeting strategies offer a viable treatment option for SLE.

In contrast to a similar immunological disease type, rheumatoid arthritis, for which a wide range of approved monoclonal antibodies or their derivatives (infliximab, adalimumab, golimumab, tocilizumab, rituximab, certolizumab pegol) are available as add-on therapeutic options [26], only one biologic drug, belimumab, has achieved marketing approval for treatment of SLE by global regulatory authorities and rendered only marginal improvement

in patient outcomes over standard of care (mainly corticosteroids or immunosuppressants) in clinical practice [3, 27, 28]. Biologics indicated for rheumatoid arthritis, such as rituximab, are often prescribed off-label to SLE patients who fail to respond to several standard therapies or other biologic treatments [29]. However, systematic evaluation of the pharmacokinetic/pharmacodynamic profiles of these biologics in patient populations with SLE has been limited [29]. It is critical to improve the understanding of the pharmacokinetic/pharmacodynamic properties of biologics used off-label to guide dosing in patients with SLE.

4.1 Interferon Pathway-Targeting Agents

Type I IFN, which promotes B cell differentiation and autoantibody production, plays an important role in the pathogenesis of SLE [30, 31]. Since the serum concentration of type I IFN is very low and difficult to detect in patients, its activity is assessed by measuring messenger RNA (mRNA) expression of type I IFN-inducible genes, also known as type I IFN-inducible gene signature [32]. It was found that the levels of type I IFN-inducible gene signature correlate with disease activity or may predict SLE flares [32]. About 70–80 % of adult patients with SLE had an elevated type I IFN-inducible gene signature [31]. Over-expression of the type I IFN-inducible gene signature was found in nearly 100 % of pediatric patients with SLE [31]. Thus, blocking of type I IFN activity or signaling at the innate phase of SLE development should be an essential part of SLE therapy.

4.1.1 Anifrolumab—Anifrolumab is an investigational human monoclonal antibody that binds to subunit 1 of the type I IFN receptor (IFN- α receptor 1), inhibiting the activity of all type I IFNs, including IFN- α , IFN- β , and IFN- ω [33]. Anifrolumab is currently the only drug candidate in development that targets the type I IFN receptor pathway for SLE. Positive results were received from a phase IIb randomized, placebo-controlled trial (RCT), which demonstrated that anifrolumab significantly reduced disease activity as measured by multiple clinical endpoints [34].

4.1.1.1 Clinical Pharmacokinetics/Pharmacodynamics: A phase IIb RCT (MI-CP1013) in adult patients with moderate to severe SLE ($n = 305$) revealed that anifrolumab exhibited greater than dose-proportional pharmacokinetic exposure as the intravenous dosage increased from 300 mg every 4 weeks to 1000 mg every 4 weeks (Table 2) [35], which was in agreement with a previous small-scale, phase II study (AZD3461C) in adult Japanese patients with SLE ($n = 17$) [36]. The greater than dose-proportional pharmacokinetic behavior was consistent with the TMDD of monoclonal antibodies that target membrane-bound receptors [37, 38], which involved progressive saturation of the receptor sink and subsequent internalization into the cells [39]. There was no difference in the pharmacokinetics between patients who were type I IFN-inducible gene signature positive and those who were negative [35]. Expression of type I IFN-inducible gene signature in whole blood decreased following anifrolumab administration in patients with a positive type I IFN-inducible gene signature (70.5 % of all patients), with a nearly similar degree of IFN gene signature inhibition achieved for both dosage arms [35]. This probably explains the lack of dose response in efficacy as reflected by the clinical endpoint analysis [34]. This phenomenon might seem contradictory to the nonlinear pharmacokinetic characteristics

observed between the two dosages, which indicated incomplete occupation of the target receptors. In a study of lupus-predisposed mice, it was suggested that the effectiveness of anti-IFN- α receptor antibody treatment did not require complete receptor blockade, but rather reduction of receptor availability below a certain threshold level, to achieve maximum inhibition of the IFN gene signature [40]. In other words, the receptor availability threshold that led to the maximum inhibition effect was already reached in the 300 mg dosage group (and further increase in the dosage may increase the occupation of IFN- α receptors up to saturation), which continued to show non-linear pharmacokinetic behavior without changing the pharmacodynamic effect as observed in the MI-CP1013 trial. Treatment efficacy was similar or more pronounced in patients with a high IFN gene signature, confirming the treatment strategy of targeting the IFN- α receptor pathway [34]. Results demonstrated near-maximum and sustained inhibition of the type I IFN-inducible gene signature by anifrolumab and supported selection of the 300 mg every 4 weeks dosage for the phase III trials.

4.2 B Cell Pathway-Targeting Agents

B cells play a central role in the pathogenesis of SLE as they produce autoantibodies that propagate a series of chain reactions leading to a varying degree of organ damage [27]. Depletion of self-reactive B cells through cluster of differentiation 20 (CD20) signaling blockade could be one approach for SLE therapy [27]. BLyS and APRIL belong to the tumor necrosis factor ligand super-family and play critical roles in B cell growth, survival, and maturation [4]. Additionally, APRIL upregulates co-stimulatory molecules on B cells and potentiates autoreactive B cell activities [41]. It has been reported that serum levels of BLyS are elevated in 50–70 % of SLE patients and ~40 % of SLE patients have increased APRIL levels [4]. Levels of these cytokines were positively correlated with disease activity and presence of anti-dsDNA autoantibodies [4]. Targeting these two cytokines is another reasonable SLE therapy strategy.

4.2.1 Rituximab—Rituximab is a chimeric anti-CD20 monoclonal antibody that inhibits B cell proliferation and survival [42]. It is the first anti-cancer antibody approved by the US Food and Drug Administration (FDA) in 1997 [43]. It is widely used as the backbone of treatment for patients with hematologic malignancies and is also prescribed off-label to SLE patients [29]. This off-label use made it the top-selling drug that achieved the highest revenue (US\$170 million) in the SLE market in 2012 [25].

4.2.1.1 Clinical Pharmacokinetics/Pharmacodynamics: A phase I/II dose-escalation trial revealed that rituximab pharmacokinetics seemed linear, as judged by the dose-proportional increase in trough concentrations at 2 months, with a single dose ranging from 100 to 375 mg/m² (Table 2) [44]. It led to effective B cell depletion, defined as a peripheral CD19⁺ B lymphocyte count <5 cells/ μ L, in a majority of patients with moderately active SLE (11 of 17) [44]. In these patients, significant improvement in the Systemic Lupus Activity Measure (SLAM) score was observed at 2 and 3 months compared with baseline ($P = 0.0016$ and $P = 0.0022$, respectively) and this improvement continued for 12 months [44]. Six of 17 patients developed human anti-chimeric antibodies at a level 100 ng/mL, which were associated with African American ancestry, higher baseline SLAM scores, less effective B cell

depletion, and lower serum rituximab concentrations at 2 months. Although it implied that rituximab may be more immunogenic in active SLE than in lymphoma [45], the low dose used in the majority of patients in this study may have contributed to the increased frequency of human anti-chimeric antibodies [44]. Data on the clinical significance of these human anti-chimeric antibodies were limited [46], but there were concerns over increased clearance of rituximab and the consequent lower drug exposure, which was significant at 2 months in this study [44]. Rituximab therapy was well-tolerated in this small patient population [44]. In a phase II/III RCT in 257 patients with moderate to severe SLE, rituximab depleted B cells but did not significantly improve the clinical outcome in the large cohorts, except in the African American/Hispanic subgroup [47]. The therapeutic failure may be attributed to the aggressive background treatment and use of stringent clinical endpoints [47]. Although the RCTs did not confirm a superiority of rituximab in SLE, observational studies have shown good response rates in severe SLE manifestations or refractory forms [48]. Rituximab is still prescribed off-label to SLE patients in light of experience-based medicine [29].

4.2.2 Belimumab—Belimumab, a human monoclonal antibody against soluble BLyS, demonstrated efficacy using the SLE Responder Index (SRI)-4 scoring system in large RCTs in patients with active SLE [49, 50], which led to its regulatory approval by the US FDA and the European Medicines Agency for treatment of autoantibody-positive SLE patients [51]. It is the first approved biologic for SLE (2011) and is still the only approved disease-modifying biologic for SLE so far. Belimumab is approved for intravenous infusion at a dose of 10 mg/kg on days 0, 14, and 28 and then every 28 days.

4.2.2.1 Clinical Pharmacokinetics/Pharmacodynamics: A phase I RCT in 70 patients with mild to moderate SLE demonstrated the linear pharmacokinetics of belimumab within the intravenous dose range of 1 to 20 mg/kg [52]. Similar to other fully human antibodies, belimumab exhibited a long terminal elimination half-life (8.5–14.1 days), slow clearance (5.6–7.3 mL/day/kg), and small volume of distribution at steady state (69.2–111.7 mL/kg) [52]. There were significant reductions in median percentages of CD20⁺ B cells in patients treated with belimumab versus placebo [52]. SLE disease activity was not improved after a single dose or two doses of belimumab.

4.2.2.2 Population Pharmacokinetic Modeling: The population pharmacokinetic modeling based on pooled data from phase I–III trials in a total of 1603 SLE patients showed that belimumab pharmacokinetics were best described with a two-compartment model with first-order elimination from the central compartment [21]. For a typical patient with a body weight of 66.3 kg, the population-estimated central clearance was 0.215 L/day and the steady-state volume of distribution was 5.29 L, with between-patient variability of each pharmacokinetic parameter as shown in Table 3. A covariate effect of dose on the peripheral volume of distribution was found in the population pharmacokinetic analysis, which led to different steady-state volume of distributions (3.70 vs. 5.29 L) and subsequent terminal half-lives (12.5 vs. 19.4 days) for the 1 and 10 mg/kg cohorts in the phase III trials, respectively. This implied a potential target-mediated elimination because of the decrease in the terminal half-life for the 1 mg/kg cohort. However, this effect caused only a minor difference (<22 %) in the simulated dose-normalized serum belimumab concentrations at steady state and was

not considered clinically meaningful. With the belimumab trough concentrations being 3 orders of magnitude higher than the BLyS baseline concentrations (median 26.33 vs. 0.02647 nmol/L on day 360) for the 1 mg/kg cohort, it was considered that the TMDD did not play a substantial role in belimumab pharmacokinetics for the dosing regimens tested. Among all of the covariates that were found to be statistically significant in the final model, body size was the only covariate that was considered clinically meaningful in influencing belimumab pharmacokinetics (Table 3), providing evidence for weight-normalized dosing regimens. Belimumab was not typically eliminated through the renal route due to its molecular size (147 kDa); however, patients with high levels of proteinuria had renal leakage which rendered a clearance pathway for proteins as well as the monoclonal antibodies of similar sizes. The effect of proteinuria levels on belimumab clearance, which was considered small in the patient population included in this study (<6 g/day at screening), could potentially be clinically relevant in patients with nephropathy of very high proteinuria levels (> 12 g/day) and may justify a dose increment [21].

4.2.2.3 Route of Administration: The phase I study in 118 healthy subjects reported that the absolute bioavailability of belimumab ranges from 74 to 82 % following single or multiple subcutaneous injections up to 240 mg, implying that subcutaneous belimumab was well-absorbed [53]. The maximum serum concentrations were observed 3.9–5.9 days post-subcutaneous injections. The terminal half-life was comparable between the subcutaneous (15.9–20.3 days) and intravenous routes (18.2 days). The occurrence of anti-belimumab antibodies was uncommon: 3.4 % of patients (three in single-dose groups, one in the multiple-dose group) had persistent positive anti-belimumab-binding antibodies and none developed neutralizing antibodies to belimumab. However, no definitive conclusion could be made with regard to the neutralizing nature of immunogenicity due to a potential issue with the sensitivity of the neutralization assay [54]. The belimumab 200 mg weekly subcutaneous injection was well-tolerated without unexpected adverse events [53]. These results were then further confirmed in a randomized study in healthy Japanese subjects ($n = 16$) taking a single dose of belimumab 200 mg administered by subcutaneous injection or intravenous infusion [55]. The 200 mg weekly subcutaneous dosing was selected for the subsequent phase III RCT (BLISS-SC [Belimumab International SLE Study—Subcutaneous]) in patients with autoantibody-positive SLE ($n = 836$, 94 % female) [53]. Positive results showed that belimumab 200 mg administered weekly via subcutaneous injection plus standard of care resulted in significantly greater reductions in disease activity scored by the SRI-4 at week 52 than placebo plus standard of care (60.8 vs. 48.5 %; $P = 0.0011$), indicating the promise of the belimumab subcutaneous formulation as an administration alternative [56].

4.2.3 Blisibimod—Blisibimod is a polypeptide protein (peptibody) consisting of two identical polypeptides, each with two BLyS-binding domains, and a human IgG1 constant region (Fc) [57]. It is a potent BLyS antagonist that binds to both cell surface-expressed and soluble BLyS. The phase IIb RCT (PEARL-SC) in 547 patients with moderate to severe SLE reported that the highest dose of subcutaneous blisibimod 200 mg weekly led to significantly improved clinical responses compared with placebo, as judged by the SRI-5

scoring system, supporting the continuous development of blisibimod as a therapeutic option for SLE [58].

4.2.3.1 Clinical Pharmacokinetics/Pharmacodynamics: A phase Ia single-dose RCT ($n = 54$) and a phase Ib multiple-dose RCT ($n = 63$) showed that blisibimod exhibited dose-proportional pharmacokinetics after subcutaneous (1–3 mg/kg) or intravenous (1–6 mg/kg) administration in subjects with mild SLE (93 % female) [59]. Intravenous blisibimod serum concentration–time profiles were biphasic with an initial distribution phase followed by a slow elimination phase. After single and four weekly subcutaneous injections, the median $t_{\max}$ ranged from 1.96 to 2.04 days post-dose, implying slow absorption after subcutaneous dosing. Blisibimod showed similar half-lives (7.9–12.0 days) across the dose range of 1.0–6.0 mg/kg by either intravenous or subcutaneous administration as a single or multiple doses. The half-lives of 0.1 mg/kg as a single dose or 0.3 mg/kg as multiple doses were significantly lower than those of 1–3 mg/kg in the subcutaneous dosing groups ($P < 0.001$ or $P < 0.05$, respectively), indicating a potential TMDD at the lower doses. In the phase Ib trial, there was a statistically significant decrease in total B cell counts in patients treated with subcutaneous blisibimod 1 or 3 mg/kg compared with the placebo group after day 100 ($P = 0.01$). For these patients, the constituency of the B cell pool also changed, as evidenced by a decrease in the percentage of naïve B cells (52–76 % decrease from baseline after day 100; $P = 0.06$), as well as a transient elevation in the memory B cell population percentage with the greatest effect on IgD⁺CD27⁺ B cells (53–154 % increase from baseline at days 15–42; $P = 0.02$) compared with the placebo group [59]. These changes in the pharmacodynamic effects were also evident in the subsequent phase II trial which reported significant reductions in total B cell counts ($P < 0.001$) and anti-dsDNA antibodies ($P < 0.001$) by week 24 in pooled subcutaneous blisibimod treatment arms (100 or 200 mg once weekly or 200 mg every 4 weeks) compared with placebo [58]. No imbalances in serious adverse events or infections were reported for blisibimod compared with placebo [58].

4.2.4 Atacicept—Atacicept is a human recombinant fusion protein that contains the extracellular, ligand-binding portion of the receptor TACI (transmembrane activator and calcium modulator and cyclophilin-ligand interactor) fused to the modified Fc portion of human IgG1 [41]. It inhibits the activities of BLYS and APRIL, the dual blockade of which suggests higher potency than blocking BLYS alone such as with belimumab. The phase II/III RCT in 461 patients with moderate to severe SLE showed no difference in flare rates or time to first flare between subcutaneous atacicept 75 mg and placebo both administered twice weekly for 4 weeks followed by weekly injections for 48 weeks [12]. Treatment with atacicept 150 mg suggested a benefit outcome; however, this arm was discontinued prematurely due to two deaths from pneumonias, raising concerns regarding the infection risk [12].

4.2.4.1 Clinical Pharmacokinetics/Pharmacodynamics: A phase Ib RCT in 24 patients with mild to moderate SLE revealed that free and total atacicept concentration–time profiles displayed multiphasic behavior by the intravenous route [60]. Atacicept exhibited non-linear pharmacokinetic characteristics across the dose range of 3–18 mg/kg, with a median terminal half-life ranging from 27 to 32 days for free atacicept and 46 to 85 days for total

atacept [60]. The serum concentrations of atacept-BLyS complex showed a saturated (less than dose-proportional) increase with dose [61]. It demonstrated a marked effect in reducing B cells and Ig levels, with the greatest reduction seen in the 9 mg/kg two-dose cohort, which showed a maximum 55 % reduction from baseline for mature B cell counts and a maximum 41 % decrease from baseline for the IgM level. Comparison of the pharmacodynamic results between the 18 mg/kg single-dose cohort and the 9 mg/kg two-dose cohort indicated a greater response when the same total dose was split into two injections given 3 weeks apart. Atacept was well-tolerated systemically and locally except for mild injection-site reactions [60].

4.2.4.2 Route of Administration: Atacept by subcutaneous administration had a fairly rapid absorption process with a similar median $t_{\max}$ of 1 day for both free and total atacept. It also exhibited non-linear pharmacokinetics due to saturable binding between atacept and its ligands [61]. The estimated bioavailability of the subcutaneous injection was approximately 30–40 %. The same dose administered by either the subcutaneous or intravenous route yielded similar biological activity in reducing Ig concentrations [61]. This phenomenon may have a ‘kinetic’ explanation as similar atacept-BLyS complex concentration–time profiles were observed in the same dose cohorts by either subcutaneous or intravenous administration, indicating a similar extent of BLyS inhibition and subsequent pharmacodynamic effects. This finding could inform the dosing regimen design for the future phase II studies.

4.3 T Cell Pathway-Targeting Agents

Abnormal expression of signaling molecules on their surface and defective signal transduction pathways are important hallmarks of T lymphocyte dysfunction in SLE [62]. T and B cells can signal to each other via several molecules expressed on their surface [62]. The CD40 ligand (CD40L), a co-stimulatory molecule present on T cells, interacts with CD40 on B cells. CD40L is an important modulator of inflammation and key regulator of T cell-dependent activation of B cells. Blockage of CD40–CD40L interaction may decrease the magnitude of T cell-dependent–humoral autoreactive responses [14]. Another T cell signaling molecule, an inducible co-stimulator (ICOS), binds to its ligand B7-related protein-1 (B7RP-1, ICOS ligand [ICOSL]) and supports B and T cell activation in the context of antigen presentation [62]. Blockade of the ICOS/ICOSL pathway may be efficacious in treating SLE.

In addition, other T cell-targeting treatments for SLE include antibodies to cytokines and their receptors, such as interleukin-6 (IL-6), IL-6 receptor, and IFN- γ . Several studies suggested that IL-6 is an important part of immunopathology of SLE [63]. SLE patients have increased levels of serum IL-6, which correlates with disease severity [64, 65]. SLE patients could benefit from neutralization of IL-6 activity or blocking of the IL-6 receptor. IFN- γ is a critical cytokine for shaping the adaptive arm in autoimmune conditions [66]. Neutralization of IFN- γ activity could also be beneficial for SLE treatment.

4.3.1 CDP7657—CDP7657, a PEGylated Fab portion of an anti-CD40L IgG1 antibody, was designed to prevent interaction between activated T cells and B cells by blocking the

CD40L on activated T cells [14]. In contrast to previously tested anti-CD40L IgG1 antibodies, it does not carry the Fc moiety, which is thought to be a critical factor for the onset of the thromboembolic events by facilitating crosslinking between platelets, and its substitution with a PEG moiety could shield against the unwanted interaction in the systemic circulation.

4.3.1.1 Clinical Pharmacokinetics/Pharmacodynamics: A first-in-human phase I RCT in healthy individuals ($n = 28$) or patients with SLE ($n = 17$) demonstrated that CPD7657 exposure increased in a dose-proportional manner across the dose range of 0.5–60 mg/kg administered by the intravenous route [14]. The disposition was biphasic, with individual terminal half-lives ranging from 6.3 to 16.1 days for healthy subjects (0.5–5 mg/kg) or 8.6 to 14.6 days for patients with SLE (5–60 mg/kg). The terminal half-lives appeared to be dose independent. There were no marked differences in the pharmacokinetic parameters of CDP7657 between healthy subjects and patients with SLE. A low level of anti-CDP7657 antibody was detected in the majority of healthy subjects and patients with SLE who received a single dose of CDP7657 above 5 mg/kg, whereas no relationship between anti-CDP7657 antibody response and CDP7657 plasma concentrations were found [14]. Most reported adverse events were mild or moderate in intensity. Two healthy individuals reported serious adverse events, one of which was an infusion-related reaction in a patient in the 5 mg/kg cohort. One patient with SLE (60 mg/kg cohort) experienced three serious adverse events, one of which was treatment-related herpes zoster infection. No thromboembolic events were reported. CDP7657 was considered to be well-tolerated and the findings supported further investigation of CDP7657 as a therapy for SLE [14].

4.3.2 AMG 557—AMG 557 is a human IgG2 monoclonal antibody that binds to B7RP-1 and inhibits its interaction with ICOS. Blockade of the B7RP-1/ICOS pathway may prevent T cell differentiation, cytokine production, and T cell-dependent help for B cells, which could be efficacious in treating SLE.

4.3.2.1 Clinical Pharmacokinetics/Pharmacodynamics: A phase I multiple-dose RCT in 56 subjects with mild, stable SLE demonstrated that the serum exposure of subcutaneous AMG 557 increased greater than dose proportionally from 6 to 70 mg and approximately dose proportionally from 70 to 210 mg [67]. This phenomenon was consistent with the involvement of TMDD through saturable binding to B7RP-1 in the vascular space (nonlinear pharmacokinetics) at lower doses plus the uptake by the RES (linear pharmacokinetics) at high doses. The B7RP-1 target occupancy by AMG 557 was dose dependent and reached maximum observed levels (>90 %) after multiple administrations of AMG 557 every 2 weeks at a dose of 140 mg or greater [67]. During the course of therapy, patients received an intradermal injection of the neoantigen keyhole limpet hemocyanin (KLH) to stimulate an immunological response in the form of antibody production. Patients in the treatment group showed a significant and selective reduction in the anti-KLH IgG response ($P = 0.0044$), but not in the anti-KLH IgM response, compared with the placebo group, consistent with the biology of targeting the ICOS pathway [67]. No consistent effect on disease activity or SLE biomarkers was observed in these patients with mild, stable SLE. The tolerability of multiple doses of AMG 557 up to 210 mg was considered acceptable as serious adverse event rates

were similar in treatment and placebo groups (12 vs. 14 %) [67]. This study supports further development of AMG 557 for treatment of SLE.

4.3.3 AMG 811—AMG 811 is a human IgG1 monoclonal antibody that selectively targets and neutralizes human IFN- γ . There was clinical evidence that the levels of IFN- γ , or chemokines whose expression is upregulated by IFN- γ , such as IFN- γ -induced protein 10 (CXCL10), are increased in SLE patients [68, 69]. CXCL10 has been shown to be an independent predictor of future disease flare in SLE [70]. Therefore, blocking IFN- γ by AMG 811 may improve disease outcome in patients with SLE.

4.3.3.1 Clinical Pharmacokinetics/Pharmacodynamics: Two phase I studies in subjects with mild, stable SLE receiving single ($n = 26$) or multiple doses ($n = 28$) of AMG 811 2–180 mg subcutaneously or 60 mg intravenously reported that it exhibited linear pharmacokinetics within the dose range of 2–180 mg [71, 72]. AMG 811 given by subcutaneous injection was slowly absorbed with a median $t_{\max}$ of 4–14 days. The mean terminal half-life ranged from 12 to 21 days with no trend observed in the half-lives over the doses. The bioavailability by the subcutaneous route was estimated to be approximately 30 % [72]. Single or multiple doses of AMG 811 modulated IFN- γ -associated gene expressions and reduced serum CXCL10 concentrations in a dose-dependent and reversible manner [71, 72]. No influence of AMG 811 on disease activity was observed in these patients with mild, stable SLE. AMG 811 showed acceptable safety profiles, which supports its further evaluation as a biologic therapy for SLE.

4.3.3.2 Population Pharmacokinetic-Pharmacodynamic Modeling: A mechanistic Pharmacokinetic-Pharmacodynamic model was developed to assess the relationship between AMG 811, its target IFN- γ , and disease biomarker CXCL10 based on the two phase I studies mentioned in the previous section [71, 72]. AMG 811 pharmacokinetics were best described by a two-compartment model with linear elimination. The impact of TMDD on AMG 811 pharmacokinetics was negligible, partially due to the fact that the AMG 811 serum concentrations at given doses were much higher than for its target IFN- γ . The linear clearance of AMG 811 was 0.176 L/day, and the central and peripheral volumes of distribution were 1.48 and 2.12 L, respectively. Body weight was identified as a significant covariate on all distribution pharmacokinetic parameters and age as a significant covariate on central volume of distribution (Table 3) [22]. Bioavailability by subcutaneous route was estimated to be 44 %. A target-mediated disposition model with quasi-steady-state (Q_{ss}) approximation described the AMG 811 and target IFN- γ interaction reasonably (Fig. 2). The relationship between the estimated free IFN- γ serum concentration and CXCL10 serum concentration in logarithmic scales was best described by a linear model with slope and intercept estimated to be 0.197 and -0.3 , respectively [22]. The highest AMG 811 dose tested, 180 mg by subcutaneous injection, led to the largest decline in the CXCL10 serum concentration [22]. This pharmacokinetic-pharmacodynamic model allows simulations of various dosing regimens of AMG 811 which will support future clinical development.

5 Clinical Pharmacokinetic/Pharmacodynamic Relationship

As summarized in Table 2, most biologic therapeutics developed for SLE have been found to reduce the levels of the target of interest, such as total or subset of B cell counts, circulating autoantibodies (Ig) levels, expression of the type I IFN-inducible gene signature, and IFN- γ -induced protein concentration, demonstrating that the mechanisms of targeting specific pharmacologic pathways are in action. However, the history of SLE pipeline products has shown little success in demonstrating efficacy or acceptable safety profiles in advanced trials. Miles and Pope [73] compared the success rates of recent SLE RCTs with rheumatoid arthritis RCTs and found 25 and 100 % positive outcomes, respectively. This reflects the complexity of SLE disease management and challenges in the development of SLE therapeutics, which could potentially benefit from early clinical PK/PD evaluations. For example, epratuzumab is a humanized monoclonal antibody targeting CD22, which is uniquely expressed on B cells [74]. Epratuzumab showed linear pharmacokinetic characteristics with a terminal half-life of approximately 13 days; however, there was no trend observed between doses and total B cell (CD20⁺) counts [75]. The phase IIb trial also found no correlation between dose and clinical response [76]. It was speculated that the positive signals in the pharmacodynamic marker or clinical response was statistical noise rather than a true pharmacological effect [77]. Subsequent phase III trials (EMBODY 1 and 2) found no significant improvement in treatment response in patients who received epratuzumab over those who received placebo, all in addition to standard therapy [78]. The disease burden may influence the dose–response relationship in biologic therapy, which necessitates dosing adjustments in patients with high disease activity. As a higher amount of antigens present leads to increased target-mediated clearance, patients with high disease activity are subject to lower exposure to biological treatment and subsequent treatment failure [26]. For example, rontalizumab is a humanized IgG1 monoclonal antibody that targets IFN- α subtypes [31]. A phase I study in adults with mildly active SLE showed that rontalizumab had a dose-proportional pharmacokinetic profile within a dose range of 0.3–10 mg/kg [79]. There was a rapid decline in IFN-regulated gene expression in the 3 and 10 mg/kg intravenous cohorts [79]. No apparent reduction in IFN-inducible proteins, anti-dsDNA, or anti-extractable nuclear antigen autoantibodies was observed [79]. The subsequent phase II study reported a lack of response in patients with high IFN signature expression, which could partially be due to dose inadequacy in that subpopulation [80]. Increased doses are needed in patients with more severe disease.

Exploring the concentration–adverse event relationship may inform the causes of adverse events in clinical studies. Sifalimumab is an investigational human IgG1 monoclonal antibody against IFN- α that exhibits linear pharmacokinetics with a half-life of approximately 20 days [36, 81, 82]. A phase Ib study (MI-CP152) in 120 adult patients with SLE supported fixed monthly dosing as none of the significant covariates identified in the population pharmacokinetic model, such as body weight and IFN gene signature, were considered clinically relevant because they explained <7 % of between-subject variability in pharmacokinetic parameters [83]. The subsequent phase IIb study in patients with moderate to severe SLE ($n = 431$) met the primary endpoint of reduced SLE disease activity across multiple clinical measures; however, a noticeable increase in the incidence of herpes zoster

infections was observed [84]. Sifalimumab was discontinued from development. There is a need to further investigate the concentration–adverse event relationships to understand the onset of toxicity in clinical use.

6 Population Pharmacokinetic/Pharmacodynamic Modeling

The population pharmacokinetics of monoclonal antibodies such as belimumab and AMG 811 were best described by a two-compartment model with central clearance and a steady-state volume of distribution ranging from 0.176 to 0.215 L/day and 3.60 to 5.29 L, respectively (Table 3). The between-subject variability in clearance was 26.4 and 36 %, respectively, and the between-subject variability in volume of distribution was 19.9 and 48 %, respectively. The addition of body size measures into the population pharmacokinetic models led to clinically meaningful reduction in between-subject variability. In the case of AMG 811, a TMDD model adequately described the relationship between the AMG 811 and IFN- γ serum concentrations, and the IFN- γ concentration was positively correlated with the concentration of the disease biomarker CXCL10 [22]. The development of linked pharmacokinetic-pharmacodynamic modeling incorporating SLE disease biomarkers or clinical scores, such as SRI-n, could be used in dosing regimen simulation and optimization.

7 Immunogenicity

Immunogenicity, the production of antidrug antibodies against biologics, may originate from the biologic molecular structure, suboptimal dosing, or temporary treatment discontinuation [85]. Initial low biologic concentrations are associated with a higher occurrence of immunogenicity [86]. Antidrug antibodies bind to the biologic drug and can form immune complexes just like the target–drug complex, leading to the accelerated clearance of biologics and underexposure of the patients to the treatment. This phenomenon partially explains the loss of patients' response to treatment over time [87]. It has been suggested that co-medications with immunosuppressants, which suppress the production of antidrug antibodies, decrease the risk of immunogenicity with its systematic, scheduled use [87]. Adjusting the dosing of biologics to a targeted concentration, which keeps the biologics “in excess” in circulation, may also prevent the immunogenicity of biologics [85].

8 Therapeutic Drug Monitoring

The highly variable pharmacokinetic/pharmacodynamic relationship in SLE treatment may contribute to treatment failure partially due to under-exposure. Therapeutic drug monitoring (TDM) is routinely used in the care of inflammatory diseases, which has shown improved clinical outcomes and reduced treatment costs in small-scale studies [88]. For example, Pouw et al. [89] investigated the relationship between the adalimumab trough concentration and clinical efficacy in patients with rheumatoid arthritis after 28 weeks of follow-up, and results showed that adalimumab trough concentrations, which were heavily influenced by concomitant methotrexate use, were sufficient to achieve an adequate clinical response (mean improvement of disease activity score in 28 joints by 2) in the range of 5–8 $\mu\text{g/mL}$ [89]. The clinical pharmacokinetic/pharmacodynamic relationship is influenced by patient factors and disease burden, indicating that TDM could benefit the dosing of biologics

prescribed for the treatment of SLE, as has been seen with inflammatory disease [88]. For instance, Vital et al. [90] reported that rituximab was effective in SLE and the clinical responses, assessed by global BILAG index, were closely correlated with B cell numbers [90]. Efforts should be made to establish the relationship between clinical response/disease biomarker and biologic exposure for the treatment of SLE involving biologics that are already on the market. TDM could also be utilized to help maintain the biologic agent within the target concentration range to decrease the risk of onset of immunogenicity [85].

9 Special Populations

As SLE mostly affects women of child-bearing age and it may flare during pregnancy and the postpartum period in 13–65 % of patients [91], it is of significant clinical importance to study SLE management involving the use of biologics in pregnant women. Because FcRn facilitates the placental transfer of mother's IgG to the fetus, it also results in fetal exposure to biologics with an Fc region during the perinatal period. In a preclinical study, belimumab crossed the placenta with mean concentrations in umbilical cord blood or amniotic fluid approximately 4- or 34-fold lower than the maternal blood in pregnant monkeys receiving a 5 or 150 mg/kg dose every 2 weeks throughout gestation, respectively [92]. Belimumab was present in breast milk at low concentrations in two female adult monkeys in the 150 mg/kg dose group [92]. Belimumab led to decreased B cell counts in the peripheral blood of mothers and infants. It was concluded that belimumab was well-tolerated at pharmacologically active dose levels throughout pregnancy. A case report of one woman who was on belimumab for the entire course of her pregnancy showed well-controlled SLE symptoms, although the baby was born with a mild Epstein's anomaly [93]. Data from a larger pregnancy registry are needed to further assess the safety of biologics in pregnancy.

10 Dashboard Systems for Individualized Dosing

In clinical practice, a fixed dose was usually adopted for subcutaneously administered biologics and the weight-normalized dose was frequently used for intravenously delivered biologics (Table 2). It should be noted that the relationship between clearance of the biologics and body weight is usually less than linear, indicating that mg/kg dosing may lead to under-exposure in patients with low body weight and over-exposure in patients with high body weight compared with that in patients typical of the studied population [87]. Mould and Dubinsky [94] summarized that the biologics, mainly monoclonal antibodies and their structural derivatives, exhibit a theoretical “U-shaped” dose-response curve, as a low dose leads to antidrug antibody formation and a high dose results in severe adverse events such as infection and cancer. If the patient shows no response from biologic therapy or loses response over time, the treatment needs to be optimized or switched to another therapy.

More personalized approaches identified patient characteristics predictive of clinical outcomes and utilized this information to optimize dosing regimens to individual patients [95]. By including patient demographics (age, body weight, etc.) and baseline disease biomarkers, these personalized approaches may align well with population pharmacokinetic/pharmacodynamic modeling [87]. The increase in the use of web-based software such as dashboard systems could enable the integration of patient characteristics with

pharmacometric models. This, in combination with Bayesian adaptive control using individual data obtained from TDM, could generate real-time treatment recommendations for clinical care providers [94].

11 Conclusion

SLE is one of the most heterogeneous and complex diseases that involves multiple immunological pathways and the effectiveness of the currently approved therapy needs to be improved. A wide selection of biologic agents that selectively target one or more immune system molecule(s) are under investigation. Given the high failure rates in late-stage clinical trials, it is crucial to establish the relationship between pharmacokinetics and efficacy/adverse events using pharmacokinetic/pharmacodynamic modeling to inform clinical drug development. The pharmacokinetic/pharmacodynamic relationships of biologics are strongly influenced by several patient factors including body size, immunogenicity, as well as disease characteristics. Understanding the components that influence the pharmacometric relationships, facilitated by the implementation of model-based therapeutic drug management, will facilitate the precision dosing of biologics to improve the clinical outcomes of SLE treatment.

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Key Points

A broad range of biologic agents that selectively target one or more immune system pathways are under investigation to offer future choices of safer and more effective treatments for systemic lupus erythematosus. Subcutaneous administration offers dosing flexibility to standard intravenous administration.

Highly variable pharmacokinetic/pharmacodynamic relationships are attributed to patient factors, disease burden, and immunogenicity, which affect the clinical responses and clinical trial outcomes in drug development. Investigation into special populations, such as pregnant women, is needed to inform clinical use.

Dosing regimen optimization may be achieved using pharmacokinetic/pharmacodynamic models that incorporate patient characteristics with Bayesian adaptive feedback along with individual information collected from therapeutic drug monitoring.

Fig. 1.

Schematic presentation of SLE pathogenesis and targeting pathways of potential or approved SLE biologic therapies. SLE patients develop defective clearance of apoptotic cells, resulting in increased levels of dsDNA, ssDNA, or other apoptotic cell material circulating in the bloodstream [4]. Antigen presenting cells, mainly dendritic cells and B cells, are activated by these self-antigens and produce increased levels of inflammatory cytokines, including type I IFN [4]. Inflammatory cytokines induce maturation of antigen presenting cells, leading to self-antigen presentation to T cells. Primed autoreactive T cells crosstalk to B cells, which in turn produce autoantibodies against self-antigens [4]. Other cytokines predominantly produced by myeloid cells, such as BLyS and APRIL, stimulate B cell proliferation and eventually autoantibody production [4]. Autoantibodies bind to self-antigens and form the immune complexes, which get deposited to various tissues and cause organ damage [4]. SLE pathogenesis is summarized into 3 major pathways: the IFN pathway (*blue line*), B cell pathway (*orange lines*), and T cell pathway (*green line*), with biologic therapeutics (*yellow rectangles*) targeting the receptors (*short lines*) or cytokines (*green rectangles*) involved in each pathway. Detailed mechanisms of action are discussed in Sect. 4 of this article. *APRIL* a proliferation-inducing ligand, *BAFF* B cell-activating factor belonging to the tumor necrosis factor family, *BAFF-R* BAFF receptor, *BCMA* B cell maturation antigen, *BCR* B cell receptor, *BLyS* B lymphocyte stimulator (also known as *BAFF*), *CD* cluster of differentiation, *CD40L* CD40 ligand, *dsDNA* double-stranded DNA, *ICOS* inducible T-cell co-stimulator, *ICOSL* inducible T-cell co-stimulator ligand, *IFN* interferon, *IFN-αR* interferon-α receptor, *IL* interleukin, *IL-6R* interleukin-6 receptor, *MHCII* major histocompatibility complex class II molecules, *SLE* systemic lupus erythematosus, *ssDNA* single-stranded DNA, *TACI* transmembrane activator and calcium modulator and cyclophilin-ligand interactor

Fig. 2.

Schematic representation of the pharmacokinetic/pharmacodynamic structural model of AMG 811, IFN- γ , and CXCL10. The pharmacokinetics of AMG 811 were best described by a two-compartment model with sequential zero-order (D_1), first-order absorption (K_a), and first-order elimination. Absolute bioavailability (F_1) was estimated by simultaneously analyzing SC and IV pharmacokinetic data. R and RC represent free IFN- γ and AMG 811–IFN- γ complex compartments, respectively. The production and degradation of IFN- γ was assumed to follow the zero-order synthesis kinetics (K_{syn}) and the first-order elimination (K_{deg}), respectively. The AMG 811–IFN- γ binding affinity was estimated by quasi-steady-state approximation with the constant (K_{ss}) calculated as $(K_{off}^+ - K_{met})/K_{on}$, where K_{on} , K_{off} , and K_{met} were the drug–target association rate constant, dissociation rate constant, and drug–target complex elimination rate constant, respectively. CXCL10 expression was induced by free IFN- γ in a linear relationship for their log-transformed values (reprinted and adapted with permission from Chen et al. [22]. Copyright 2015 Springer). CL clearance, $CXCL10$ IFN- γ -induced protein 10, $CXCL10 \sim f(R)$ CXCL10 concentration change was a function of free IFN- γ , IFN interferon, IV intravenous, Q inter-compartment clearance, R_0 baseline IFN- γ concentration, SC subcutaneous, V_c central volume of distribution, V_p peripheral volume of distribution

Table 1

Biologic therapeutics indicated for systemic lupus erythematosus: approved, off-label use, and pipeline products with pharmacokinetic/pharmacodynamic information available

Biologics	Molecule type	Mechanism of action	Targeting pathway	Development status
Belimumab	Human IgG1 monoclonal antibody	Anti-BLyS (soluble BLyS)	B cells	IV marketed; SC phase III
Rituximab	Chimeric IgG1 monoclonal antibody	Anti-CD20	B cells	Off-label use
Anifrolumab	Human IgG1 monoclonal antibody	Anti-IFN- α receptor	IFN	Phase III
Blisibimod	Recombinant fusion protein	Anti-BLyS (soluble and membrane-bound BLyS)	B cells	Phase III
Atacicept	Recombinant fusion protein	Anti-BLyS, anti-APRIL	B cells	Phase II
AMG 557	Human IgG2 monoclonal antibody	Anti-B7RP-1	T cells	Phase I
AMG 811	Human IgG1 monoclonal antibody	Anti-IFN- γ	T cells	Phase I
CDP7657	PEGylated antibody fragment	Anti-CD40L	T cells	Phase I

Data correct as at November 2015

APRIL a proliferation-inducing ligand, *B7RP-1* B7-related protein-1, *BLyS* B lymphocyte stimulator, *CD20* cluster of differentiation 20, *CD40L* CD40 ligand, *IFN* interferon, *Ig* immunoglobulin, *IV* intravenous, *PEGylated* polyethylene glycol conjugated, *SC* subcutaneous

Table 2
Clinical pharmacokinetics/pharmacodynamics of biologic therapeutics for the treatment of systemic lupus erythematosus

Biologics	Phase	Patients	Route	Dosing regimen	Pharmacokinetic properties	Pharmacodynamic properties
IFN pathway-targeting agents						
Anifrolumab [35]	IIb	305 adults with moderate to severe SLE	IV	300 or 1000 mg every 4 weeks for 1 year	Non-linear pharmacokinetics; <i>C_{rough}</i> was 18.8 ± 10.9 µg/mL for the 300 mg every 4 weeks arm and 115.0 ± 62.9 µg/mL for the 1000 mg every 4 weeks arm on day 169	Expression of type I IFN-inducible gene signature decreased in patients with positive type I IFN-inducible gene signature, median signature neutralization ranges were 85.2–89.7 % for 300 mg every 4 weeks and 86.8–91.9 % for 1000 mg every 4 weeks between days 29 and 365
B cell pathway-targeting agents						
Rituximab [44]	I/II	17 patients with moderately active SLE	IV	Single infusion of 100 mg/m ² (low dose), single infusion of 375 mg/m ² (intermediate dose), or four weekly infusions of 375 mg/m ² (high dose, full lymphoma dose)	Linear pharmacokinetics; geometric means (range) of rituximab concentrations at 2 months were $0.10 (<0.02-4.82)$, $0.32 (<0.02-7.80)$, and $9.36 (0.36-22.50)$ µg/mL for the low-, intermediate-, and high-dose groups, respectively	A majority of patients (11 of 17) had effective B cell depletion and a significantly improved SLAM score at 2 and 3 months compared with baseline ($P < 0.0016$ and $P < 0.0022$), respectively
Belimumab [21, 52, 53]	III	1122 patients with autoantibody-positive SLE	IV	1 and 10 mg/kg every 2 weeks for the first 3 doses and every 4 weeks up to 72 weeks	Linear pharmacokinetics; for the 10 mg/kg group (approved regimen), the terminal $t_{1/2}$ ranged from 8.5 to 14.1 days, mean CL approximately 7 mL/day/kg, and mean V_{ss} 69–112 mL/kg	In the high-dose belimumab group, 17 % of patients who were seropositive for anti-dsDNA titers at baseline reverted to negative anti-dsDNA by week 52 compared with 6 % in the placebo group ($P = 0.0008$) [49]. Treatment group was also associated with sustained reduction in CD20 ⁺ B cells ($P = 0.001$) [50]
	I	57 patients with autoantibody-positive SLE	IV	1, 4, 10, and 20 mg/kg as a single infusion or 2 infusions 21 days apart	Linear pharmacokinetics; mean terminal $t_{1/2}$ ranged from 8.5 to 14.1 days, mean CL approximately 7 mL/day/kg, and mean V_{ss} 69–112 mL/kg	There was significant decrease in median percentages of CD20 ⁺ B cells in patients receiving a single dose of belimumab vs. placebo (day 42: $P = 0.0042$; day 84: $P = 0.0036$) or 2 doses of belimumab vs. placebo (day 105: $P = 0.0305$)
	I	118 healthy subjects	IV, SC	Single IV dose of 240 mg, single or four weekly SC doses up to 240 mg	Linear pharmacokinetics; for the weekly SC dose of 200 mg (selected for phase III), t_{max} (mean $\pm$ SD) 5.5 ± 1.2 days, CL/F 4.2 ± 1.2 mL/day/kg, terminal $t_{1/2}$ 19.8 ± 4.9 days, and bioavailability 77.9 %	Mean IgG level was generally similar after single SC or IV dose or multiple SC doses. Four subjects had persistent positive immune responses (anti-belimumab antibody)
Blisibimod [59]	Ia, Ib	117 patients with mild SLE that was stable/inactive at baseline (phase Ia, $n = 54$, phase Ib, $n = 63$)	IV, SC	Single SC dose of blisibimod 0.1, 0.3, 1, or 3 mg/kg or 1, 3, or 6 mg/kg IV (phase Ia); four weekly doses of blisibimod (0.3, 1, or 3 mg/kg SC or 6 mg/kg IV (phase Ib))	Approximate dose-proportional pharmacokinetics; four weekly doses at 3 mg/kg SC had a t_{max} mean (range) of 2.04 (0.02–7.08) days, and C_{max} $t_{1/2}$ and CL/F (mean $\pm$ SD) of 34.6 ± 8.84 µg/mL, 10 ± 2.4 days, and 1.4 ± 0.4 L/day, respectively	Multiple-dose treatment with blisibimod produced a decrease in the number of naïve B cells and a transient relative increase in the memory B cells, leading to an overall 30 % reduction in total B cells by 160 days after the first dose

Biologics	Phase	Patients	Route	Dosing regimen	Pharmacokinetic properties	Pharmacodynamic properties
Atacicept [60, 61]	Ib	24 patients with mild to moderate SLE	IV	Single dose: 3, 9, or 18 mg/kg; or multiple doses: 9 mg/kg as 2 doses given 3 weeks apart	Non-linear pharmacokinetics; median terminal t_1 was 27–32 days for free atacicept, 46–85 days for total atacicept, and 65–408 days for atacicept-BLyS complex. Median CL for free atacicept was 6.8–7.7 L/day	Atacicept induced an initial transient increase followed by a reduction in mature and total B cells. Ig levels also decreased rapidly with the greatest reductions seen for IgM from 9 mg/kg, 2-dose cohort
T cell pathway-targeting agents						
CDP7657 [14]	I	Healthy individuals ($n = 28$) or patients with SLE ($n = 17$)	IV	Single dose of 0.004–5 mg/kg for healthy subjects and 5–60 mg/kg for patients with SLE	Linear pharmacokinetics; t_1 was 6.25–16.1 days across the dose groups 0.5–5 mg/kg for healthy individuals and 8.6–14.6 days for patients with SLE. CL ranged from 0.25 to 0.57 L/day in healthy participants and 0.26 to 0.56 L/day in patients with SLE; V_d ranged from 3.56 to 9.07 L in healthy individuals and 4.05 to 8.17 L in patients with SLE	Low anti-CDP7657 antibody titers were detected in the majority of CDP7657-treated participants. No apparent association was found between anti-CDP7657 antibody response and CDP7657 plasma concentrations
AMG 557 [67]	I	56 subjects with mild, stable SLE	SC	7 doses of 6–210 mg given every 2 weeks	Greater than dose-proportional pharmacokinetics from 6 to 70 mg and approximately dose-proportional pharmacokinetics from 70 to 210 mg	Significant and selective reduction in the anti-KLH IgG response was observed with AMG 557 treatment
AMG 811 [22, 71, 72]	I	Subjects with mild, stable SLE in single-dose ($n = 26$) or multiple-dose ($n = 28$) trials	IV, SC	Single dose of 2–180 mg SC or 60 mg IV; multiple doses of 6–60 mg SC given monthly for a total of 3 doses	Linear pharmacokinetics; median t_{max} was 4–14 days for the SC doses, mean terminal t_1 ranged from 12 to 21 days after IV and SC dosing	AMG 811 led to a dose-dependent and reversible modulation of the expression of genes associated with IFN- γ signaling as well as reduction in CXCL10 levels

Anti-dsDNA anti-double-stranded DNA, *BLyS* B lymphocyte stimulator, *CD20* cluster of differentiation 20, *CL* clearance, *CL/F* apparent clearance, *C_{max}* maximum concentration, *C_{trough}* trough concentration, *CXCL10* IFN- γ -induced protein 10, *IFN* interferon, *Ig* immunoglobulin, *IV* intravenous, *KLH* keyhole limpet hemocyanin, *SC* subcutaneous, *SD* standard deviation, *SLAMF* systemic Lupus Activity Measure, *SLE* systemic lupus erythematosus, $t_{1/2}$ elimination half-life, t_{max} time to maximum concentration, V_d volume of distribution, V_{SS} volume of distribution at steady state

Table 3

Population pharmacokinetic/pharmacodynamic models of biologic therapeutics for the treatment of systemic lupus erythematosus

Biologics	Structural model	Pharmacokinetic parameters (RSE%)	Covariates	Pharmacodynamic parameters (RSE%)	Clinical implication
Belimumab ^a [21]	2C linear CL	CL 0.215 L/day (1.95) V_c 2.56 L (0.961) Q 0.459 L/day (10.8) V_p 2.73 L (4.03) BSV on CL 26.4 % (6.27) BSV on V_c 19.9 % (28.4) BSV on V_p 31.1 % (35.2)	Body weight ↑, CL ↑, V_c ↑; body mass index ↑, V_c ↓	In comparison with placebo, belimumab caused sustained reductions in anti-dsDNA antibody levels, as well as increases in C3 and C4 concentrations, with a more pronounced effect observed in the 10 mg/kg dose group. Reductions in B cells (CD20 ⁺) were observed at weeks 24, 52, and 76 ($P < 0.001$) [50]	The covariate effect of body size measures was accounted for by the weight-normalized dosing
AMG 811 ^b [22]	2C linear CL	CL 0.176 L/day (6) V_c 1.48 L (35) Q 0.66 L/day (60) V_p 2.12 L (7) K_a 0.178 day ⁻¹ (22) F_1 44 % (70) D_1 0.12 day (16) BSV on CL 36 % (15) BSV on V_c 48 % (19) BSV on Q 79 % (28) BSV on V_p 47 % (12) BSV on D_1 110 % (70)	Body weight ↑, CL ↑, V_c ↑, Q ↑, V_p ↑; age ↑, V_c ↑	A TMDD model with Q_{ss} approximation adequately described AMG 811 and target IFN- γ interaction. Free serum IFN- γ CXCL10 concentrations in logarithmic scales were best described by a linear model with slope 0.197 (25) and intercept -0.3 (67)	Largest reduction of serum CXCL10 was achieved at highest AMG 811 SC dose of 180 mg

2C two-compartment model, *anti-dsDNA* anti-double-stranded DNA, *BSV* between-subject variability, *C3* complement component 3, *C4* complement component 4, *CD20* cluster of differentiation 20, *CL* central clearance, *CXCL10* IFN- γ -induced protein 10, *D₁* duration of zero-order kinetics, *F₁* fraction available for systemic absorption, *IFN* interferon, *IV* intravenous, *K_a* absorption rate constant, *Q* inter-compartment clearance, *Q_{ss}* quasi-steady-state, *RSE* relative standard error, *SC* subcutaneous, *SLE* systemic lupus erythematosus, *TMDD* target-mediated drug disposition, *V_c* central volume of distribution, *V_p* peripheral volume of distribution, ↑ indicates increase, ↓ indicates decrease

^aBelimumab data were collected from phase I–III trials in a total of 1603 patients with autoantibody-positive SLE receiving doses of 1, 4, 10, or 20 mg/kg

^bAMG 811 data were from two phase I trials involving 54 patients with mild SLE receiving a single dose of 2–180 mg SC or 60 mg IV or multiple doses of 6–60 mg SC given monthly for a total of 3 doses