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Review

Advances in the treatment of systemic lupus erythematosus: From back to the future, to the future and beyond

Renaud Felten[a,b,c,*], Florence Scher[d], Jean Sibilia[a,b,e], François Chasset[f,g], Laurent Arnaud[a,b,e]

[a] Service de rhumatologie, hôpitaux universitaires de Strasbourg, 67200 Strasbourg, France
[b] Université de Strasbourg, centre national de référence RESO-Lupus, 67000 Strasbourg, France
[c] Laboratoire d'immunologie, immunopathologie et chimie thérapeutique, institut de biologie moléculaire et cellulaire (IBMC), CNRS UPR3572, 67000 Strasbourg, France
[d] Service de pharmacie-stérilisation, hôpitaux universitaires de Strasbourg, 67000 Strasbourg, France
[e] Laboratoire d'immunorhumatologie moléculaire, Inserm UMR_S1109, 67000 Strasbourg, France
[f] Sorbonne université, faculté de médecine, Sorbonne université, 75013 Paris, France
[g] Service de dermatologie et allergologie, hôpital Tenon, AP–HP, 75020 Paris, France

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ABSTRACT

There have been many advances in the diagnosis and therapeutic management of systemic lupus erythematosus (SLE) over the past decades. Following more than eleven centuries of therapeutic uncertainty, the discovery of the therapeutic properties of glucocorticoids is without any doubt one of the most significant advance in the field of autoimmune diseases. The many progresses made by rapidly growing chemical industry of the 19th century chemistry have allowed the identification of valuable therapeutic compounds such as anti-malarials, cyclophosphamide, azathioprine, cyclosporine and later mycophenolate mofetil, which have all profoundly changed the face of the disease. A very visible consequence of this is the profound improvement in the prognosis of the disease, with 10-year survival rates of more than 90% in most dedicated centres. Following the development of biotherapies in rheumatoid arthritis, the late 20th century has slowly opened a new era for the treatment of SLE, that of targeted therapies. With the approval of belimumab in 2011 and 74 targeted therapies in clinical development, we may expect great changes in the therapeutic management of SLE. Those molecules target inflammatory cytokines or chemokines and their receptors, B cells or plasma cells, intracellular signalling pathways, B/T cells co-stimulation molecules, interferons, plasmacytoid dendritic cells, as well as various other targets of interest. Current challenges are now slowly shifting from whether some new drugs will be available to how to select the most adequate drug (or drug combination) at the patient-level.
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1. Introduction

There have been many advances in the diagnosis and therapeutic management of Systemic Lupus Erythematosus (SLE) since the miraculous cure of Eracle, bishop of Liège, at St-Martin's shrine in the French city of Tours around the year 855 [1]. Following more than eleven centuries of therapeutic uncertainty, the discovery of the therapeutic properties of glucocorticoids is without any doubt one of the most significant advance in the field of autoimmune diseases (Table 1). The many progresses made by rapidly growing chemical industry of the 19th century chemistry have allowed the identification of valuable therapeutic compounds such as anti-malarials, cyclophosphamide, azathioprine, cyclosporine and later mycophenolate mofetil, which have all profoundly changed the face of the disease. A very visible consequence of this is the profound improvement in the prognosis of the disease, with survival rates of more than 90% at ten years in most dedicated centres. Following the development of biotherapies in rheumatoid arthritis (RA), the late 20th century has opened a new era for the treatment of SLE, that of targeted therapies [2]. With the approval of belimumab in 2011 and currently more than 74 targeted therapies in clinical development [2], we may expect great changes in the therapeutic management of SLE. With that, remains the need to identify laboratory tools [3] that may help us unfold the heterogeneity of the

* Corresponding author at: Service de rhumatologie, centre national de référence des maladies auto-immunes et systémiques rares, hôpital de Hautepierre, 1, avenue Molière, BP 83049, 67098 Strasbourg cedex, France.
E-mail address: renaud.felten@chru-strasbourg.fr (R. Felten).

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Table 1
Timeline of drug development in SLE.

Year	Development
855	Miraculous cure of Eracle's (Bishop of Liège) lupus at Saint-Martin's shrine in Tours, France
1230	Rolando da Parma distinguishes *noli me tangere* (lesions on the face) from *Lupula* (lesions in the lower limbs). No cure known at that time
1894	Payne reports the efficacy of quinine extracts
1950	Hench is was awarded the Nobel Prize for the therapeutic use of glucocorticoids in inflammatory disease
1951	Page reports the efficacy of the antimalarial mepacrine
1953	First report of chloroquine to treat SLE
1954	Dubois reports the efficacy of cyclophosphamide in SLE [6]
1956	First series about the use of hydroxychloroquine in SLE [7]
1967	First use of methotrexate, azathioprine and tacrolimus in SLE
1981	First use of cyclosporine in SLE
1992	NIH trial assessing the efficacy of IV cyclophosphamide in severe LN [30]
1997	First use of tacrolimus in SLE
2000	First reports of mycophenolate mofetil in SLE
2001	First use of rituximab in SLE
2002	Euro-lupus trial assessing the efficacy of low dose of IV cyclophosphamide in LN [32]
2010	Failure of the EXPLORER rituximab trial
2011	Approval of belimumab by the FDA and EMA
2011	ALMS trial assessing the efficacy of mycophenolate mofetil in LN [35]
2012	Failure of the LUNAR rituximab trial
2016	Failure of the ILLUMINATE-1 and 2 tabalumab trials [60,61]
2017	Failure of the EMBODY epratuzumab trial [59]
2018	74 targeted therapies under clinical development in the SLE pipeline [2]

disease and improve the selection of the best therapeutic option, at the patient-level [4]. In this review, we will analyze how currently available treatments have paved the way for future more targeted treatments in SLE.

2. Back to the future

In 1818, Willan, the founder of modern dermatology, states, "I can mention no medicine [...] of any service in the cure of it" [5]. In 1894, Payne reports the efficacy of quinine extracts to cure the disease. In 1951, Page reported the efficacy of the antimalarial mepacrine, showing a marked improvement of cutaneous lesions in 17 out of 18 patients. Following a first use in RA in 1948, Hench was awarded the Nobel Prize for the therapeutic use of glucocorticoids in inflammatory diseases. The efficacy of cyclophosphamide in SLE was first reported in 1954 by Dubois [6]. Finally, the first series about the use of hydroxychloroquine in SLE was reported by Lewis in 1956 [7]. These developments paved the way for more targeted treatments.

2.1. Glucocorticoids

Glucocorticoids (GCs) have revolutionized the treatment of inflammation in the 1950's. They suppress the production of pro-inflammatory cytokines and inhibit leukocyte recruitment by decreasing endothelial cell permeability and adhesion molecule production. Nowadays, GCs remain the mainstay of SLE treatment. The use of GCs has led to an improved survival among high risk patients [8]. Up to 88% of SLE patients are treated with GCs according to long-term follow-up of SLE cohorts, 57% to 86% receiving continuous treatment [9]. Despite more than 60 years of experience, no consensual guidelines can be formulated regarding the optimal doses of GC according to disease manifestations, based on current literature reports [9,10]. One of the main challenges in treating SLE patients remains the reduction of glucocorticoid dose as they have been strongly linked to increase damage accrual [11]. To avoid side effects, the cumulative GC-dose should be kept as low as possible. In clinical practice tapering is possible in many, but not, all SLE patients and based on the physician's own insight and experience.

2.2. Anti-malarials: hydroxychloroquine, chloroquine and mepacrine

Infusions of the bark of the Peruvian cinchona tree have been used since long years for both their antimalarial and anti-inflammatory properties. The active agents, quinine and cinchonine were isolated in the 1950's. Due to their many beneficial effects, anti-malarials, and especially hydroxychloroquine, (HCQ) have become the mainstay of SLE treatment. Chloroquine (CQ) is mainly used in case of HCQ intolerance or failure. HCQ and chloroquine have several effects on the immune system, including the increase of lysosomal pH in antigen-presenting cells, and the blocking of toll-like receptors (TLR) on plasmacytoid dendritic cells. Anti-malarials have shown a very good efficacy against arthritis and specific skin lesions [12]. Their withdrawal is associated with an increased risk of flare [13]. They also reduce organ damage [14,15]. Adherence to anti-malarials is a critical point in the management of SLE patients [16]. A very low blood concentration of HCQ < 200 ng/mL is a good marker of poor adherence and may be useful to discriminate between failure of HCQ and non-adherent patients [17].

During the recent years, numerous advances have been made regarding the optimization of the use anti-malarials, such as demonstrating the deleterious role of smoking [18], validating the blood concentration threshold (> 750 ng/mL) prospectively [19], and better defining the strategy to be used in case of side effects [20]. In Cutaneous Lupus Erythematosus (CLE), in case of failure of HCQ, a switch to CQ seems effective in more than 50% of cases [20]. Moreover HCQ has shown several positive effects on thrombosis and infection risk, leading to an improved global care of lupus patients as these are important causes of morbidity in SLE.

2.3. Methotrexate

Methotrexate is an antimetabolite agent, inhibiting the enzyme dihydrofolate reductase, which plays an important role in the synthesis of purine nucleotides and thymidylate. By this way it induces the apoptosis of inflammatory cells. Methotrexate also reduces inflammatory cytokines.

Methotrexate was initially developed in the 1950s as a cancer therapy. Its first use in low doses was reported in 1967 in SLE patients, then in the 1970's. First controlled clinical trial in 1999 showed that methotrexate 15 to 20 mg/week for 6 months was effective in controlling cutaneous and articular activity of SLE and allowed prednisone sparing [21]. In a retrospective study of 43 CLE patients treated with methotrexate 15 to 25 mg one per week 98% shown improvement of cutaneous lesions particularly for discoid and subacute CLE patients. Recent European guidelines for CLE recommended the use of methotrexate in second line of systemic treatment after failure of anti-malarials [22]. Most evidence for efficacy on SLE-specific manifestations has been reported for articular and cutaneous manifestations. Thus, methotrexate is mainly use in case of articular symptoms to reduce joint pain and swelling and sparing the dose of glucocorticoids. There is significant teratogenicity associated with methotrexate use and pregnancy is therefore contra-indicated.

2.4. Azathioprine

Azathioprine (AZA) is a derivative of 6-mercaptopurine that acts as an antimetabolite agent by affecting purine nucleotide synthesis and metabolism. AZA was first used in 1967 to treat SLE. Quickly, it has been confirmed that AZA was useful in SLE to improve treatment using only prednisone. The prednisone require-

ment of patients receiving AZA was also decreased compared to that of control subjects [23]. Furthermore using AZA to treat patients with neuropsychiatric lupus and severe renal disease led to decreased hospitalizations and increased survival rate [24,25]. In daily practice, AZA is mostly used as an additional immunosuppressive treatments as well as a GC-sparing agent. In fact, most evidence for its current use stems from LN trials. In addition, it has been shown that the exposure to AZA during pregnancy is safe and lacks of teratogenicity in patients with SLE [26] compared to others immunosuppressive drugs used in SLE.

2.5. Cyclophosphamide

Cyclophosphamide (CYC) is an inactive pro-drug metabolized via the cytochrome-P450 leading to the active metabolite phosphoramide mustard and the inactive metabolite acrolein. The mustard metabolites act as an alkylating agent and react with purines, forming DNA adducts and cross-links therefore inhibiting proliferative responses of both T and B lymphocytes.

CYC has had a profound impact over the prognosis of the disease, especially in case of severe manifestations such as lupus nephritis or CNS involvement [27,28]. The efficacy of oral cyclophosphamide was demonstrated in a randomised controlled trial (RCT) in 1978 [29] and further confirmed for intravenous CYC in the subsequent NIH trial [30]. Further studies have demonstrated the beneficial effect of the combined high-dose intravenous GCs and CYC regimen [31] in lupus nephritis. NIH regimen consists of 500–1000 mg/m^2 CYC IV monthly for 6 months, and then quarterly for at least 12 months. The major limitation of the use of the NIH protocol in lupus nephritis is its untoward side effects, which include infection, ovarian and bladder toxicities, leukopenia and an increased risk of malignancy. In 2002, Houssiau reported the use of the Euro-Lupus regimen [32], which consists of a fixed dose of 500 mg CYC IV, every two weeks for 3 months. This led to a major advance conferred by the use of reduced-dose strategies. Long-term data are available [33]. There is significant teratogenicity associated with cyclophosphamide use and pregnancy is therefore contra-indicated.

2.6. Mycophenolate mofetil

Mycophenolic acid (MPA) was first discovered in 1913 and first used clinically in the 1970s as an immunosuppressant to prevent organ transplantation rejection. From the late 1990s a pro-drug, mycophenolate mofetil (MMF), was developed and more recently, enteric-coated mycophenolate sodium (EC-MPS). MMF is an inactive pro-drug that is metabolized to MPA. As a potent, selective, non-competitive, and reversible inhibitor of inosine monophosphate dehydrogenase, MPA inhibits de novo synthesis of guanosine nucleotides without being incorporated into DNA. Therefore, MPA has cytostatic effects on T and B lymphocytes and inhibits antibody formation. It prevents the intercellular adhesion of lymphocytes and monocytes to endothelial cells, and may inhibit recruitment of leukocytes into sites of inflammation.

In SLE, following preliminary reports in 2000–2005 and the large RCTs by Ginzler et al. in 2005 and by Appel et al. in 2009, the efficacy of MMF for the induction treatment of lupus nephritis was well-established. For the maintenance regimen, data against CYC were obtained by Contreras et al. in 2004 [34] and expanded against AZA by Houssiau in 2010 [33] and Dooley et al. in 2011 [35]. As with antimalarials, recent advances have shown the importance of assessing the exposure to the active metabolites of MMF in SLE, such as by assessing the Area Under the concentration/time Curve (AUC) of mycophenolic acid, its main active metabolite (AUC $\geq$ 35 have been associated with decreased disease activity) [36]. There is significant teratogenicity associated with MMF use and pregnancy is therefore contra-indicated.

2.7. Calcineurin inhibitors: cyclosporine A and tacrolimus

Discovery of cyclosporine in 1971 began a new era in immunopharmacology. It was the first immunosuppressive drug that allowed selective immunoregulation of T cells without excessive toxicity. Cyclosporine was isolated from the fungus Tolypocladium inflatum and was first investigated as an anti-fungal antibiotic. Borel discovered its immunosuppressive properties in 1976 and subsequently revolutionized the management of organ transplantation, with a first use in this indication in 1980. The immunosuppressive activity of cyclosporine depends on its binding to cyclophylin, an intracellular protein, which leads to the inhibition of T-helper lymphocytes with the suppression of the production of IL-2 (and its receptor) and IFN-γ.

First report in SLE was made in 1981, showing an interesting efficacy but significant side effects. No patient was able to take the drug for longer than seven weeks. The BILAG multicentre RCT demonstrated a GC-sparing effect of cyclosporin A but this effect was not superior to that of AZA [37]. Cyclosporine A was shown to be as effective as CYC in the CYCLOFA-LUNE trial for sequential induction and maintenance in patients with proliferative lupus nephritis with preserved renal function [38].

Tacrolimus was discovered in 1987 and first approved by the FDA in 1994 for use in transplantation. It is a macrolide immunosuppressant produced by the soil fungus *Streptomyces tsukubaensis*. Tacrolimus binds to the FKBP-12 intracellular protein and forms a complex which inhibits the calcineurin. It inhibits NF-κB involved in gene transcription blocking the production of pro-inflammatory cytokines.

Its first use in the context of SLE was reported in 1997, mostly as an additional treatment of lupus nephritis, with interesting results but significant side effects like hypertension. Tacrolimus has been compared to mycophenolate mofetil [39]. Tacrolimus was non-inferior to MMF, when combined with prednisolone, for induction therapy of active lupus nephritis. Nevertheless, for maintenance therapy for 5 years, there was a trend of higher incidence of renal flares and renal function decline with the tacrolimus regimen compared to the azathioprine regimen [39]. EULAR/ERA-EDTA recommendations for the management of adult and paediatric lupus nephritis place tacrolimus as an alternative therapy in the management of refractory renal disease in lupus [40]. Recent Japanese and Chinese studies have indicated a potential benefit of tacrolimus as a substitute for or in addition to CYC or MMF [41,42]. It deserves further investigation in view of their additional effect on podocytes by reducing proteinuria and the promising data from Asian patients.

2.8. Thalidomide and Lenalidomide

Thalidomide displays immunosuppressive and anti-angiogenic activity. It inhibits release of TNF-α from monocytes, and modulates other cytokine action. Thalidomide has been used since 1982 to treat refractory case CLE. Its efficacy in CLE is clear [43] with an overall rate of response of 90% but a rate of withdrawal related to adverse events of 24% including an important increase in the risk of thrombosis [44] and peripheral neuropathy. In SLE, thalidomide was first investigated in a series of 3 patients in 1992 [45]. It can also be used to treat severe cutaneous manifestations of SLE with an efficacy of almost 100% but at the cost of side effects [46].

Lenalidomide is a 4-amino-glutamyl analogue of thalidomide. The drug has immunomodulatory, anti-angiogenic and anti-inflammatory properties by inhibiting the secretion of the pro-inflammatory cytokines by monocytes. In a retrospective study 88% of patients were responders without cases of new or worsening peripheral neuropathy [47]. Such as thalidomide, efficacy of lenalidomide is only suspensive and dose should be tapered to reach a minimum effective dose. Lenalidomide seems to have

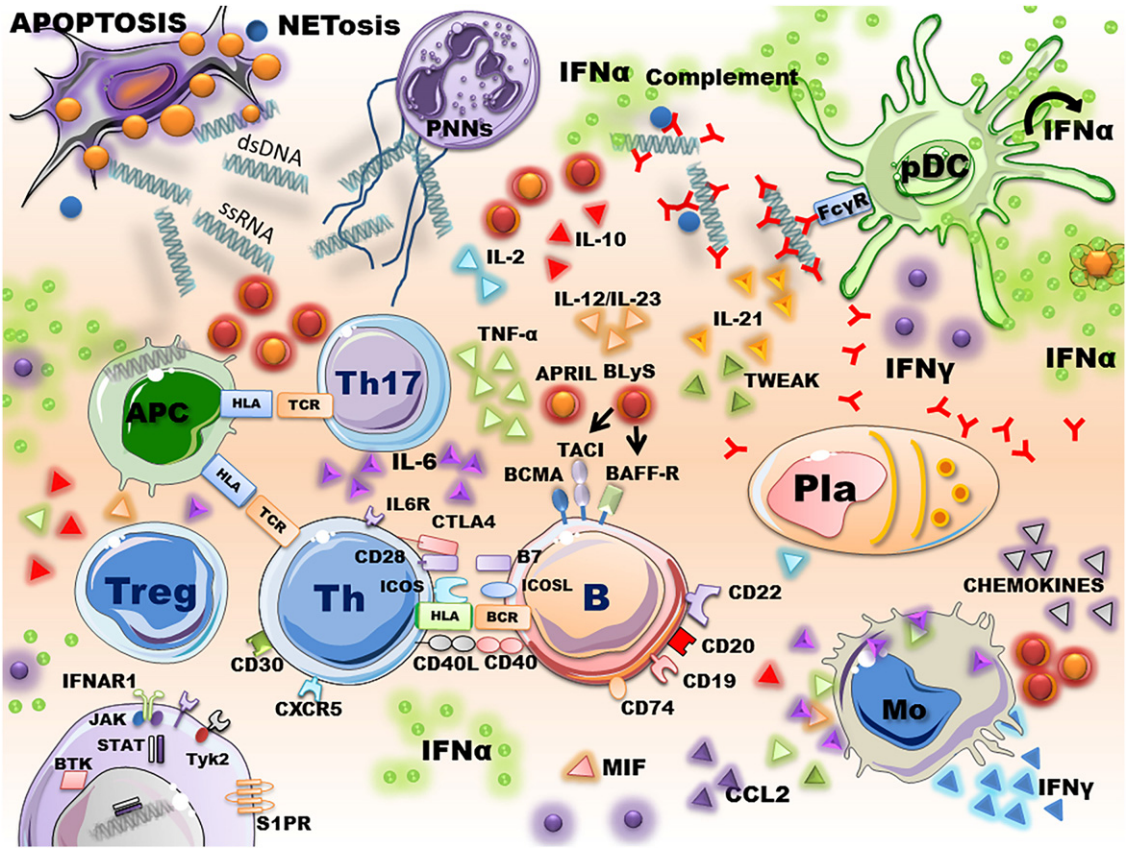

Fig. 1. Pathogenesis of SLE and targets of SLE treatments.

no impact on ds-DNA antibody titer or complement levels [48] and a risk of renal flare has even been suggested in a small open-label study [49]. There is significant teratogenicity associated with thalidomide and lenalidomide use and pregnancy is therefore contra-indicated.

2.9. Rituximab

Since its initial approval for use in non-Hodgkin's lymphoma in 1997, rituximab has been used to successfully treat RA and has also been part of anti-rejection treatments for kidney transplants. Rituximab is a chimeric monoclonal Ab against the protein CD20. CD20 is widely expressed on B cells, from early pre-B cells to later in differentiation, but it is absent on terminally differentiated plasma cells. The Fc portion of rituximab mediates antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, inducing apoptosis of $CD20^+$ cells. Rituximab was first used in SLE in 2001 in single case reports. In 2002, an open study with 6 SLE patients provided sufficient evidence for the safety and possible efficacy. Thus, the use of rituximab has been investigated in several phase III RCT which did not meet their primary endpoint (LUNAR, EXPLORER). However, extensive data from registries have confirmed the interest for the drug, mostly in the context of lupus nephritis or cytopenias [50–52]. Rituximab may be useful in severe refractory acute or subacute CLE lesions but seems to have no effect on refractory discoid CLE lesions [53].

2.10. Belimumab

Increased levels of B lymphocyte stimulator (BLyS) was associated with systemic autoimmunity in animal models and significant elevations of BLyS in patients with SLE was first demonstrated in 2001 [54]. BLyS is an essential factor for B cell survival and development. Belimumab is a fully humanized mAb against BLyS also called B cell-activation factor (BAFF) that belongs to the TNF family. Administration of belimumab leads to depletion of naive, activated and $CD20^+$ B cells, and a reduction in anti-ds-DNA titers. Belimumab has been demonstrated to be effective in reducing SLE disease activity on top of standard care and delaying the time to lupus flares in phase III RCT (BLISS-52 & BLISS-76 [55,56]). It is currently the only approved biological agent for the treatment of SLE. Results from an Italian prospective cohort study shown that belimumab may have clinical benefits for acute and subacute CLE patients [57].

3. To the future, and beyond

Our group has recently published a systematic review of targeted therapies under clinical development in SLE in 17 main online registries of clinical trials [2]. From a total of 1140 trials, we were able to extract 74 distinct targeted therapies for SLE. Treatment strategies under current clinical development for SLE target inflammatory cytokines or chemokines and their receptors ($n = 17$), B cells or plasma cells ($n = 17$), intracellular signalling pathways ($n = 10$), T/B cells co-stimulation molecules ($n = 8$), interferons ($n = 7$), plasmacytoid dendritic cells (pDC) ($n = 3$), as well as various other targets ($n = 12$) (Fig. 1). The candidate drugs have reached phase I ($n = 20$), I/II ($n = 5$), Phase II ($n = 36$), phase II/III ($n = 2$), phase III ($n = 9$) and phase IV (post-marketing development, $n = 2$). The corresponding trials were completed ($n = 28$), recruiting ($n = 19$), prematurely terminated ($n = 16$), active but not recruiting ($n = 8$) and withdrawn ($n = 3$).

Table 2
Overview of SLE trials of most promising drugs in development.

Drug	Mechanisms of action	Current development phase	Current development stage	NCT number	Publication	Indications in development
Anifrolumab	Anti-IFN-α receptor monoclonal antibody (IFNAR1)	Phase 2	Complete Has results	NCT01438489	[65] 4	SLE
		Phase 3	Active, not recruiting	NCT02446899		
		Phase 3	Completed	NCT02446912		
		Phase 2	Active, not recruiting	NCT02962960		SLE skin manifestations
		Phase 3	Recruiting	NCT02794285		Long-time safety
		Phase 2	Recruiting	NCT02547922		Proliferative LN
Baricitinib	selective JAK-1 and JAK-2 inhibitor	Phase 2	Completed	NCT02708095	[66] 4	SLE
		Phase 3	Recruiting	NCT03616912		
		Phase 3	Recruiting	NCT03616964		
Low dose IL-2	Modification of the regulator/effector T cell balance	Phase 2a	Completed	NCT02084238	[64] 3	SLE
		Phase 2	Unknown	NCT02465580		
		Phase 2	Recruiting	NCT03312335		
		Not applicable	Completed	NCT02932137		
		Phase 2	Active, not recruiting	NCT02955615		
Ustekinumab	Anti-p40 (IL-12/23) monoclonal antibody	Phase 2	Active, not recruiting Has results	NCT02349061	[63] 2	SLE
		Phase 3	Recruiting	NCT03517722		

3.1. Targeting B or plasma cells

In addition to rituximab, three other anti-CD20 antibodies, with a similar mechanism of action, are currently in the SLE pipeline: obinutuzumab (recruiting phase II), TRU-015 (terminated phase I) and ocrelizumab (completed phase III [58]) which was not statistically superior to standard of care in LN. Epratuzumab targets the CD22 antigen on B cells, yielding a peripheral B cell depletion. Its efficacy was assessed in the phase III EMBODY trial [59], which did not reach its primary endpoint. SM03, another anti-CD22, has been evaluated in a phase I study. XmAb5871 targets CD19 (recruiting phase II). Milatuzumab (or hLL1) is an anti-CD74 Ab (completed phase I/II, results pending).

Besides belimumab, another anti-BAFF Ab, tabalumab has been assessed in SLE with two phase 3 trials (ILLUMINATE-1 and 2 [60,61]) but the current development of this molecule has been stopped because the primary endpoint was not reached in one of those trials. Atacicept (TACI-Ig) has undergone clinical evaluation in SLE with a terminated phase II/III study. RC-18 is a TACI-Ab fusion protein injection (recruiting phase II). Blisibimod is a fusion protein consisting of four BAFF binding domains fused to Fc (terminated phase III). AMG 570 is a bispecific Ab-peptide conjugate that targets BAFF and ICOS ligand (active phase I). Ixazomib, a proteasome inhibitor, is currently being evaluated in a recruiting phase I study.

3.2. Targeting B/T cells co-stimulation molecules

Abatacept and RG2077 (two CTLA4-Ig) have been assessed respectively in phase II/III and in phase I/II trials (results pending), respectively. Dapirolizumab, an anti-CD40 L Ab and BI 655064, an anti-CD40 Ab are assessed in recruiting phase II trials. Dapirolizumab has been the first biologic to show efficacy in a RCT for Sjogren's syndrome [62] and results in SLE are pending. MEDI-570, an anti-ICOS Ab and AMG 557, an anti-ICOSL Ab have been assessed in completed phase I trials. Theralizumab and Lulizumab pegol, two anti-CD28 Ab have been evaluated (respectively recruiting phase II and terminated phase II).

3.3. Targeting inflammatory cytokines/chemokines or their receptors

Anti-TNF have been tested in SLE with conflicting results: etanercept in lupus nephritis (NCT00447265) as well as infliximab in a phase III trial. Most teams agree that those are mostly contra-indicated in SLE because they can lead to drug-induced SLE and can worsen SLE.

Two IL-6 inhibitors, PF-04236921 and sirukumab (completed phase II) and two IL-6R antibodies: MRA 003 US (completed phase I) and vobarilizumab (active phase II) have been tested in phase I or II trials. The positive results of a phase II of ustekinumab, an IL-12/23 inhibitor, have been presented at the ACR 2017 [63] (Table 2). Another strategy, the administration of low doses IL-2 to SLE patients, which expands the Treg population with interesting modulatory effects, has been successfully tested in a completed phase II trial [64] (Table 2). Other options studied in SLE include: an anti-IL-10 Ab (active phase II), an anti-TWEAK Ab (BIIB023, terminated phase II), anti-IL-21 Abs (NNC01140006, terminated phase I and BOS 161721 recruiting phase I/II study), an anti-CD30 Ab (Brentuximab, terminated phase II), an anti-MIF Ab (imalumab, terminated phase I), emapticap pegol, which binds the human chemokine CCL2 (completed phase I), SAR 113244, an anti-CXCR5 Ab (completed phase I) and PF-06835375, a chemokine inhibitor (completed phase I).

3.4. Targeting interferons

Significant advances in our understanding of the molecular basis of innate immunity have led to identification of interferons (IFNs) and particularly IFN-α, as a central mediator in the pathogenesis of SLE. It is in 2003 that a broad IFN-I-induced gene transcript signature was identified in PBMC from SLE patients. DNA and RNA-containing Immune complexes are phagocytosed by pDC through FcγRIIa and delivered into the endosomal compartment triggering the activation of TLR-7 and TLR-9 which ultimately lead to the production of IFN-α. Four anti-IFN-α mAbs have reached clinical development (Fig. 2): rontalizumab (completed phase II), sifalimumab (completed phase II), AGS-009 (completed phase I) and JNJ-55920839 (recruiting phase I). Direct blocking of IFN-α only may not be the best strategy in SLE as IFN-β, IFN-κ and IFN type III remain active. Another promising strategy is to target directly IFN receptors rather than IFNs (Fig. 2). Anifrolumab is a monoclonal Ab directed against the subunit 1 of the type I IFN receptor (IFNAR1) for which the results of a phase III trial are pending (Table 2). IFN-α-kinoid (IFNK), a therapeutic vaccine composed of IFN-α2b coupled to a carrier protein that induces polyclonal anti-IFN-α neutralizing antibodies, is being assessed in an active phase II trial (Fig. 2).

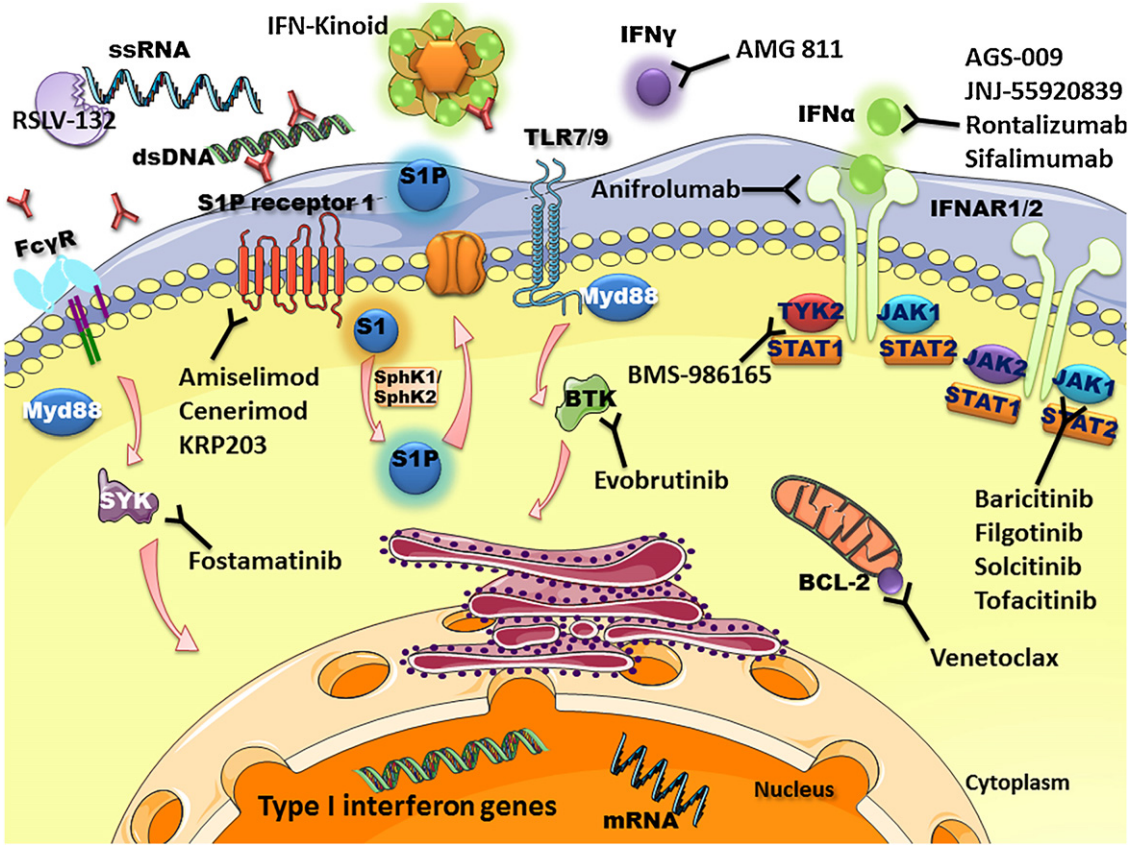

Fig. 2. pDC, IFN and downstream pathways targeting therapies.

The development of AMG 811, a human anti-IFN-γ Ab, has halted following an unsuccessful phase I study.

3.5. Targeting the intracellular signaling pathways

Therapeutic inhibitors of JAKs have appeared as potentially valuable drugs in SLE, with several molecules under clinical development such as tofacitinib (recruiting phase I/II), baricitinib (completed phase II), solcitinib (terminated phase II) and filgotinib (recruiting phase II) (Fig. 2). In a recent phase II trial, treatment with baricitinib improved the signs and symptoms of active disease in patients with systemic lupus erythematosus (SLE) who were receiving standard background therapy [66] (Table 2). The use of Baricitinib 4 mg treatment resulted in a greater proportion of patients achieving resolution of arthritis, as defined by Systemic Lupus Erythematosus Disease Activity Index-2000, than with placebo. An inhibitor of Tyrosine Kinase 2 (TYK2), BMS-986165, is reaching a recruiting phase II. Evobrutinib, a Bruton's Tyrosine Kinase Inhibitor (BTKi), is now assessed in a recruiting phase IIb study. Three treatments targeting the sphingosine-1-phosphate pathway, sphingosine-1-phosphate receptor type 1 agonists have also been evaluated: cenerimod (completed phase II), amiselimod (completed phase I) and KRP203 (completed phase II).

3.6. Targeting pDCs

Strategies targeting the plasmacytoid dendritic cells (pDC), the main producers of IFN-alpha, include the use of BIIB059 (recruiting phase II), a monoclonal Ab targeting the pDC-specific cell surface receptor BDCA2, the use of anti-CD123 monoclonal antibodies such as talacotuzumab (withdrawn phase I) and venetoclax, a BCL-2 inhibitor (completed phase I) (Fig. 2).

3.7. Other targets identified in SLE

There is also a parallel development of small molecule drugs that inhibit or interfere with other perturbations identified in SLE: laquinimod (completed phase II), paquinimod (completed phase II, pending results), rigerimod (completed phase III), iguratimod (recruiting phase II trial), edratide, a synthetic peptide (phase II, terminated); iberdomide binding cereblon (CRBN), a peptide hydrolase and a component of E3 ubiquitinin ligase complex (recruiting phase II) and INV103 (ala-Cpn10), a minimally modified version of the chaperonin 10 (completed phase I/II). In a recent phase 3 trial, rigerimod combined with standard therapy did not demonstrate a statistically significant increase in the response rate over standard care alone, and the primary endpoint of the trial was not met.

Other therapeutic options under development in SLE include an anti-C5 Ab (NNC 0151-0000-0000) (completed phase I), OMS721, an anti-MASP-2 Ab (recruiting phase II trial), omalizumab, an anti-IgE Ab (completed phase I), RSLV-132, a fully human biologic Fc fusion protein of human RNase and Fc domain of human IgG1 (Fig. 2) (recruiting phase II).

4. Conclusion

The therapeutic management and prognosis of SLE has profoundly evolved with changes in the pharmacopeia. Among the most recent evolutions in the therapeutic management of SLE is the increased recognition of the need to limit as much as possible the exposure to GCs, including the use of GC-free therapeutic regimens in some cases [67]. However, the favourable survival (> 90% at 10 years) in most dedicated centers does not hinder the fact that several gaps in the care of SLE patients remain, especially

for lupus nephritis, CNS involvement, and minorities. With more than 74 drugs in the SLE pipeline of clinical development [2], current challenges are shifting from whether some new drugs will be available to how to choose the most adequate drug (or drug combination) at the patient-level. This further increases the need to better characterize the heterogeneous spectrum of the disease. For this, the development of ultra-sensitive methods allowing the measurement of biomarkers at the femto-level is a major advance [3], although not widely available. The need to investigate biomarkers that would allow adequate prediction of response-to-therapy remains high, but when solved will allow a more rational selection of the optimal pharmacological agent within the broad pipeline of targeted therapies for SLE.

Disclosure of interest

Renaud Felten has received honoraria (not related to SLE) from AbbVie and BMS.

Florence Scher has nothing to declare.

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References

[1] Smith CD, Cyr M. The history of lupus erythematosus. From Hippocrates to Osler. Rheum Dis Clin North Am 1988;14:1–14.
[2] Felten R, Dervovic E, Chasset F, et al. The 2018 pipeline of targeted therapies under clinical development for systemic lupus erythematosus: a systematic review of trials. Autoimmun Rev 2018;17:781–90.
[3] Rodero MP, Decalf J, Bondet V, et al. Detection of interferon alpha protein reveals differential levels and cellular sources in disease. J Exp Med 2017;214:1547.
[4] Banchereau R, Hong S, Cantarel B, et al. Personalized immunomonitoring uncovers molecular networks that stratify lupus patients. Cell 2016;165:551–65.
[5] Bateman T. Practical synopsis of cutaneous diseases. Collins & Croft; 1818.
[6] Dubois EL. Nitrogen mustard in treatment of systemic lupus erythematosus. AMA Arch Intern Med 1954;93:667–72.
[7] Lewis HM, Frumess GM. Plaquenil in the treatment of discoid lupus erythematosus; a preliminary report. AMA Arch Dermatol 1956;73:576–81.
[8] Albert DA, Hadler NM, Ropes MW. Does corticosteroid therapy affect the survival of patients with systemic lupus erythematosus? Arthritis Rheum 1979;22:945–53.
[9] Mosca M, Tani C, Carli L, et al. Glucocorticoids in systemic lupus erythematosus. Clin Exp Rheumatol 2011;29:126–9.
[10] RKMAC Luijten, Fritsch-Stork RD, Bijlsma JWJ, et al. The use of glucocorticoids in systemic lupus erythematosus. After 60 years still more an art than science. Autoimmun Rev 2013;12:617–28.
[11] Apostolopoulos D, Kandane-Rathnayake R, Raghunath S, et al. Independent association of glucocorticoids with damage accrual in SLE. Lupus Sci Med 2016;3:e000157.
[12] Chasset F, Bouaziz J-D, Costedoat-Chalumeau N, et al. Efficacy and comparison of anti-malarials in cutaneous lupus erythematosus subtypes: a systematic review and meta-analysis. Br J Dermatol 2017;177:188–96.
[13] Tsakonas E, Joseph L, Esdaile JM, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. Lupus 1998;7:80–5.
[14] Petri M, Purvey S, Fang H, et al. Predictors of organ damage in systemic lupus erythematosus: the Hopkins lupus cohort. Arthritis Rheum 2012;64:4021–8.
[15] Pons-Estel GJ, Alarcón GS, McGwin G, et al. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. Arthritis Rheum 2009;61:830–9.
[16] Arnaud L, Zahr N, Costedoat-Chalumeau N, et al. The importance of assessing medication exposure to the definition of refractory disease in systemic lupus erythematosus. Autoimmun Rev 2011;10:674–8.
[17] Costedoat-Chalumeau N, Amoura Z, Hulot J-S, et al. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. Ann Rheum Dis 2007;66:821–4.
[18] Chasset F, Francès C, Barete S, et al. Influence of smoking on the efficacy of anti-malarials in cutaneous lupus: a meta-analysis of the literature. J Am Acad Dermatol 2015;72:634–9.
[19] Chasset F, Arnaud L, Costedoat-Chalumeau N, et al. The effect of increasing the dose of hydroxychloroquine (HCQ) in patients with refractory cutaneous lupus erythematosus (CLE): An open-label prospective pilot study. J Am Acad Dermatol 2016;74:693–9.
[20] Chasset F, Arnaud L, Jachiet M, et al. Changing antimalarial agents after inefficacy or intolerance in patients with cutaneous lupus erythematosus: A multicenter observational study. J Am Acad Dermatol 2018;78:107–14.
[21] Carneiro JR, Sato EI. Double blind, randomized, controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol 1999;26:1275–9.
[22] Kuhn A, Aberer E, Bata-Csörgő Z, et al. S2k guideline for treatment of cutaneous lupus erythematosus. J Eur Acad Dermatol Venereol JEADV 2017;31:389–404.
[23] Sztejnbok M, Stewart A, Diamond H, et al. Azathioprine in the treatment of systemic lupus erythematosus. A controlled study. Arthritis Rheum 1971;14:639–45.
[24] Ginzler E, Sharon E, Diamond H, et al. Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. Arthritis Rheum 1975;18:27–34.
[25] Maher JF, Schreiner GE. Treatment of lupus nephritis with azathioprine. Arch Intern Med 1970;125:293–8.
[26] Saavedra MÁ, Sánchez A, Morales S, et al. Azathioprine during pregnancy in systemic lupus erythematosus patients is not associated with poor fetal outcome. Clin Rheumatol 2015;34:1211–6.
[27] Fanouriakis A, Pamfil C, Sidiropoulos P, et al. Cyclophosphamide in combination with glucocorticoids for severe neuropsychiatric systemic lupus erythematosus: a retrospective, observational two-centre study. Lupus 2016;25:627–36.
[28] Rodrigues M, Galego O, Costa C, et al. Central nervous system vasculitis in systemic lupus erythematosus: a case series report in a tertiary referral centre. Lupus 2017;26:1440–7.
[29] Austin HA, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614–9.
[30] Boumpas DT, Austin HA, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet Lond Engl 1992;340:741–5.
[31] Gourley MF, Austin HA, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;125:549–57.
[32] Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the euro-lupus nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.
[33] Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–4.
[34] Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971–80.
[35] Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886–95.
[36] Zahr N, Arnaud L, Marquet P, et al. Mycophenolic acid area under the curve correlates with disease activity in lupus patients treated with mycophenolate mofetil. Arthritis Rheum 2010;62:2047–54.
[37] Griffiths B, Emery P, Ryan V, et al. The BILAG multicentre open randomized controlled trial comparing ciclosporin vs. azathioprine in patients with severe SLE. Rheumatol Oxf Engl 2010;49:723–32.
[38] Zavada J, Pesickova S, Rysava R, et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the cyclofa-lune study. Lupus 2010;19:1281–9.
[39] Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis 2016;75:30–6.
[40] Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771.
[41] Tanaka H, Oki E, Tsuruga K, et al. Management of young patients with lupus nephritis using tacrolimus administered as a single daily dose. Clin Nephrol 2009;72:430–6.
[42] Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant 2012;27:1467–72.
[43] Chasset F, Tounsi T, Cesbron E, et al. Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus: A systematic review and meta-analysis. J Am Acad Dermatol 2018;78:342–50.
[44] Cesbron E, Bessis D, Jachiet M, et al. Risk of thromboembolic events in patients treated with thalidomide for cutaneous lupus erythematosus: a multicenter-retrospective study. J Am Acad Dermatol 2018;79:162–5.
[45] Bessis D, Guillot B, Monpoint S, Dandurand M, Guilhou JJ. Thalidomide for systemic lupus erythematosus. Lancet 1992;339:549–50.
[46] Wang D, Chen H, Wang S, et al. Thalidomide treatment in cutaneous lesions of systemic lupus erythematosus: a multicenter study in China. Clin Rheumatol 2016;35:1521–7.

[47] Fennira F, Chasset F, Soubrier M, et al. Lenalidomide for refractory chronic and subacute cutaneous lupus erythematosus: 16 patients. J Am Acad Dermatol 2016;74:1248–51.
[48] Cortés-Hernández J, Ávila G, Vilardell-Tarrés M, et al. Efficacy and safety of lenalidomide for refractory cutaneous lupus erythematosus. Arthritis Res Ther 2012;14:R265.
[49] Braunstein I, Goodman NG, Rosenbach M, et al. Lenalidomide therapy in treatment-refractory cutaneous lupus erythematosus: histologic and circulating leukocyte profile and potential risk of a systemic lupus flare. J Am Acad Dermatol 2012;66:571–82.
[50] Ramos-Casals M, Soto MJ, Cuadrado MJ, et al. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. Lupus 2009;18:767–76.
[51] Weidenbusch M, Römmele C, Schröttle A, et al. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant 2013;28:106–11.
[52] Díaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev 2012;11:357–64.
[53] Vital EM, Wittmann M, Edward S, et al. Brief report: responses to rituximab suggest B cell-independent inflammation in cutaneous systemic lupus erythematosus. Arthritis Rheumatol Hoboken NJ 2015;67:1586–91.
[54] Zhang J, Roschke V, Baker KP, et al. Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. J Immunol 2001;166:6–10.
[55] Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721–31.
[56] Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918–30.
[57] Iaccarino L, Bettio S, Reggia R, et al. Effects of belimumab on flare rate and expected damage progression in patients with active systemic lupus erythematosus. Arthritis Care Res 2017;69:115–23.
[58] Mysler EF, Spindler AJ, Guzman R, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum 2013;65:2368–79.
[59] Clowse MEB, Wallace DJ, Furie RA, et al. Efficacy and safety of epratuzumab in moderately to severely active systemic lupus erythematosus: results from two phase III randomized, double-blind, placebo-controlled trials. Arthritis Rheumatol Hoboken NJ 2017;69:362–75.
[60] Isenberg DA, Petri M, Kalunian K, et al. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis 2016;75:323–31.
[61] Merrill JT, van Vollenhoven RF, Buyon JP, et al. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis 2016;75:332–40.
[62] Fischer B, et al. The novel anti-CD40 monoclonal antibody CFZ533 shows beneficial effects in patients with primary Sjögren's syndrome: a phase IIa double-blind, placebo-controlled randomized trial. ACR Meet Abstr n.d. https://acrabstracts.org/abstract/the-novel-anti-cd40-monoclonal-antibody-cfz533-shows-beneficial-effects-in-patients-with-primary-sjogrens-syndrome-a-phase-iia-double-blind-placebo-controlled-randomized-trial/ [accessed June 22, 2018].
[63] Efficacy and safety of ustekinumab, an interleukin 12/23 inhibitor, in patients with active systemic lupus erythematosus: results of a phase 2, randomized placebo-controlled study. ACR Meet Abstr n.d. http://acrabstracts.org/abstract/efficacy-and-safety-of-ustekinumab-an-interleukin-1223-inhibitor-in-patients-with-active-systemic-lupus-erythematosus-results-of-a-phase-2-randomized-placebo-controlled-study/ [accessed March 2, 2018].
[64] He J, Zhang X, Wei Y, et al. Low-dose interleukin-2 treatment selectively modulates CD4+ T cell subsets in patients with systemic lupus erythematosus. Nat Med 2016;22:991–3.
[65] Furie RA, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol Hoboken NJ 2017;69:376–86.
[66] Wallace DJ, Furie RA, Tanaka Y, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Lond Engl 2018;392:222–31.
[67] Tedeschi B, Arnaud L, Hie M, et al. Successful treatment of combined proliferative and membranous lupus nephritis using a full corticosteroid-free regimen. Ann Rheum Dis 2014;73:474–5.