New and future therapies: Changes in the therapeutic armamentarium for SLE

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ABSTRACT

Following better understanding of molecular pathways involved in the pathogenesis of Systemic lupus erythematosus (SLE), pharmaceutical companies have been investigating new targeted drugs for SLE. The purpose of this scoping review is to provide an updated view of the most promising targeted therapies currently in clinical development or recently approved for SLE treatment as well as of the most promising potential future therapeutic strategies in SLE.

In the past several years, two new drugs have been developed for lupus treatment along with an extended indication for belimumab. Anifrolumab, the anti-interferon medication, to treat non-renal lupus; voclosporin, a calcineurin inhibitor, for the treatment of lupus nephritis; and belimumab for lupus nephritis. More than 90 investigational drugs are currently in clinical development for SLE treatment, with various targets including inflammatory cytokines and their receptors, intracellular signaling, B cells or plasma cells, co-stimulation molecules, complement fractions, T cells,
plasmacytoid dendritic cells as well as various other immunological targets of interest. Researchers are also actively engaged in the development of new therapeutic strategies, including the use of monoclonal antibodies in combination with bispecific monoclonal antibodies, nanobodies and nanoparticles, therapeutic vaccines, utilizing siRNA interference techniques, autologous hematopoietic stem-cell transplantation and Chimeric Antigens Receptor (CAR)-T cells. The therapeutic management and prognosis of SLE have profoundly evolved with changes in the therapeutic armamentarium. With the broad pipeline of targeted treatments in clinical development and new treatment strategies in the future, current challenges are transitioning from the availability of new drugs to the selection of the most appropriate strategy at the patient level.

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a broad spectrum of clinical, laboratory, and immunological manifestations. Following better understanding of molecular pathways involved in the pathogenesis of the disease, pharmaceutical companies have been investigating new targeted candidate drugs for SLE. Following the recent publication of key pivotal phase 3 trial results, recent approvals in SLE treatment include belimumab and voclosporine for lupus nephritis and anifrolumab for moderate-to-severe SLE. Nevertheless, unfulfilled needs for the treatment of SLE are still considered. New and more effective therapeutic strategies are needed. The purpose of this scoping review is to provide an updated view of the most promising targeted therapies currently in clinical development or approved for SLE treatment as well as of the most promising new therapeutic strategies for SLE.

New drugs & extended indications for systemic lupus erythematosus

In the past several years, two new drugs have been developed for lupus treatment along with an extended indication for belimumab: 1) anifrolumab, the anti-type I interferon receptor medication, to treat non-renal lupus, 2) voclosporin, a calcineurin inhibitor, for the treatment of lupus nephritis (LN), and 3) belimumab for lupus nephritis. Below are some highlights of the data of these three new additions to SLE armamentarium.

Anifrolumab

Type I interferon (IFN) initiates immune processes by binding to the Type I IFN receptor subunit 1 on the surface of multiple cells in the innate and adaptive immune systems. Type I IFN—interferon-α/β receptor (IFNAR) binding causes dimerization, resulting in intracellular signaling. Anifrolumab binds to IFNAR and blocks receptor dimerization, inducing receptor internalization [1,2].

Anifrolumab was approved by the U.S. Food & Drug Administration (FDA) and European Medicines Agency (EMA) based on the results of three 52-week, randomized, double-blind, placebo-controlled studies, one phase two trial, MUSE, and two phase three trials known as the TULIP trials [3–6]. The study designs were similar for the pivotal phase 3 TULIP-1 and TULIP-2 trials in adults with moderate to severe SLE, both studies were randomized, placebo-controlled, and all patients continued on standard therapy [3,4]. Anifrolumab or placebo was administered intravenously once every 4 weeks plus standard therapy. Standard therapy included combinations of antimalarials, immunosuppressants, nonsteroidal anti-inflammatory drugs, and/or oral corticosteroids (OCS). Patients continued to receive their SLE therapy at stable doses, except OCS, which were tapered per protocol [3–5]. In TULIP-1, two
different doses of anifrolumab were tested: 150 mg and 300 mg. The 150 mg arm was evaluated for dose response and was not an approved dose [3–5]. In TULIP-2, only the 300 mg dose was tested [4]. In both trials, mandatory attempts to taper oral OCS to 7.5 mg or less per day between week 8 and 40 were required for patients receiving prednisone 10 mg or more per day, at baseline; tapering was permitted for patients receiving doses lower than 10 mg per day at baseline [3,4]. For all patients, OCS doses were required to be stable between week 40 and 52 [3,4]. The primary end point for TULIP-1 was the SLE Responder Index (SRI) [4] response rate at week 52, whereas in TULIP-2, the primary end point was the British Isles Composite Lupus Assessment (BICLA) response rate at week 52 [3,4]. In TULIP-1, the primary end point, SRI-4 response rate at week 52 was achieved by 49% of patients in the treatment vs 43% in the placebo arm (p = NS); the BICLA response rate was 47.1% vs 30.2% and it was a prespecified secondary end point, but not formally tested and results were descriptive. In TULIP-2, the primary end point, BICLA response rate at week 52, significantly favored anifrolumab 47.8% over placebo 31.5%, p = 0.001 [3–5]. In TULIP-2, the SRI(4) response rate 55.5% vs 37.3% was a prespecified secondary end point but was not adjusted for multiplicity; these results are descriptive. BICLA responses were achieved with anifrolumab treatment in interferon gene signature (IFNGS)-High and IFNGS-Low patients subpopulations; however, placebo responses were higher in the IFNGS-Low patients. Another prespecified end point in TULIP-2 was BICLA response sustained up to week 52 (3), the time course of the sustained BICLA response was not multiplicity adjusted, consequently the results were only descriptive; however, separation between treatment arms began approximately at week 4 and was maintained to week 52. Patients were 55% more likely to achieve a sustained BICLA response through the remainder of treatment, similar trends were noted in TULIP-1. Anifrolumab showed significant improvement of cutaneous lupus with ≥50% reduction in the Cutaneous LE Disease Area and Severity Index (CLASI) activity from baseline to week 12 reached in 49% in the anifrolumab group vs 25% in the placebo group p = 0.04. The last key secondary end point of TULIP-2 was the proportion of patients who achieved an OCS dose ≤7.5 mg/day at week 40, maintained through week 52. This end point was examined in the subgroup of patients (47%) with baseline OCS ≥10 mg/day [3,4]. More patients in the treatment arm were able to reduce OCS dosage than those in the placebo group (30%) to ≤7.5 mg/day from Week 8 to Week 40; P = 0.004(3). Across the placebo and anifrolumab 300 mg groups from all three studies, most cases of herpes zoster were mild or moderate cutaneous [4]. Of the 28 anifrolumab-treated patients who had herpes zoster, 2 had disseminated disease requiring hospitalization compared to none among patients who received placebo [3].

In a post hoc pooled analysis of the TULIP studies, a greater proportion of patients treated with anifrolumab had an improvement in the mucocutaneous, musculoskeletal, hematologic, and immunologic SLEDAI-2K domains compared to those treated with placebo; similar results were also seen in less frequently affected domains [7].

Eligible patients from the TULIP studies were enrolled in a separate long-term extension (LTE) study that further supports the efficacy and safety of anifrolumab over 4 years of follow-up. The exposure adjusted incidence rates of herpes zoster infection were 3.4 per 100 person years in the anifrolumab group and 2.8 per 100 person years in the placebo group. Patients in the combined anifrolumab 300 mg group had a mean SLEDAI-2K score of 11.4 at TULIP baseline and 5.1 at week 52, compared with the 11.3 at TULIP baseline and 6.0 at week 52 for the combined placebo group, which continued to year 4 (3). The reduction in mean SLEDAI-2K score was observed in parallel with reduction of the mean OCS dose and decreased flare rates, as well as lower accumulation of damage, measured using SLICC Damage index – SDI [3,4].

The accumulated evidence thus far shows that anifrolumab is effective and safe for the treatment of non-renal lupus, with decrease in disease activity, reduced steroid use, flare rate, and persistent safety over 4 years. As data from the clinical trials for subcutaneous anifrolumab, lupus nephritis, isolated cutaneous lupus, and pediatric lupus patients become available, we expect an increased understanding of the efficacy of anifrolumab in lupus treatment.

Belimumab

Belimumab is a recombinant human IgG-1λ monoclonal antibody that inhibits B-cell activating factor (BAFF) [8,9]. Belimumab was initially approved for the treatment of SLE in 2011 following two
phase 3 clinical trials [9–11]. Several additional studies further substantiated the efficacy and safety of belimumab.

**Belimumab in lupus nephritis**

In December 2020, the US FDA approved belimumab for the treatment of LN. Post hoc analyses of patients in these studies who had proteinuria at baseline showed decreased proteinuria and incidence of renal flares in patients treated with belimumab [12]. These observations led to the establishment of the Belimumab International Study in LN (BLISS-LN) to evaluate the efficacy and safety of belimumab plus standard therapy (mycophenolate mofetil (MMF) or cyclophosphamide–azathioprine) in patients with active LN; 448 patients were randomized 1:1 to receive IV belimumab (10 mg/kg) or placebo, in addition to standard therapy. The primary end point at week 104 was the primary efficacy renal response (a ratio of urinary protein to creatinine-urine protein creatinine ratio (UPCR) of $\leq 0.7$, an estimated glomerular filtration rate (eGFR) that was no worse than 20% below the value before the renal flare (pre-flare value) or $\geq 60$ ml per minute per 1.73 m$^2$ of body-surface area, and no use of rescue therapy). The major secondary end point was complete renal response (CRR) (UPCR $< 0.5$, an eGFR $\leq 10\%$ below the pre-flare value or $\geq 90$ ml per minute per 1.73 m$^2$, and no use of rescue therapy). At week 104, significantly more patients in the belimumab group than in the placebo group achieved a primary efficacy renal response (43% vs. 32%; odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3; $P = 0.03$) and CRR (30% vs. 20%; odds ratio, 1.7; 95% CI, 1.1 to 2.7; $P = 0.02$).

In a post hoc analysis of the BLISS-LN study, add-on belimumab was found to be most effective in improving the primary efficacy kidney response and complete kidney response in patients with Class III or IV LN and a baseline UPCR under 3 g/g.

**Voclosporin**

Voclosporin is a novel calcineurin inhibitor (CNI) that does not require therapeutic drug monitoring, does not affect MMF levels [13,14], and has a more favorable metabolic profile than other CNIs [15]. Based on positive results from the pivotal phase 2 and 3 trials, voclosporin became the first approved oral therapy in the United States for the treatment of adults with active LN in January 2021 [16]. voclosporin phase 2 AURA-LV and phase 3 AURORA 1 randomized-controlled studies with similar designs and end points enrolled 534 patients [17,18]. Both trials clinically demonstrated the efficacy of 23.7 mg voclosporin BID added to a background of MMF and low-dose glucocorticoids. The primary efficacy outcome was CRR at approximately 1 year of treatment, comprising week 48 data from AURA-LV and week 52 data from AURORA 1. Both trials showed significantly higher CRR in treated patients.

However, at 52 weeks, the change in the SLEDAI-2K score was similar between the standard-of-care and the voclosporin group ($-5.5$ vs. $-6.0$, $p = 0.227$), which raises the possibility that voclosporin renal effect is mostly provided by its antiproteinuric effect. Furthermore, kidney histological analysis indicates similar improvement between the voclosporin and the standard-of-care treatment group [19], although this analysis is limited by its small sample size.

The pooled analysis of these combined data showed that more patients achieved a CRR at 1 year in the voclosporin group (43.7%) than in the control group (23.3%), OR 2.76, $p < 0.0001$. Adverse events (AEs) were similar in both groups; 91.4% voclosporin and 87.2% control. Most AEs were mild/moderate, the most common were infections and infestations (62.2% voclosporin, 54.9% control) and gastrointestinal (45.3% voclosporin, 35.3% placebo). No new or unexpected safety signals were detected. This integrated analysis further demonstrates the efficacy and safety of voclosporin in the treatment of LN across the diverse racial and ethnic groups studied.

A significantly higher proportion of the voclosporin group achieved a partial renal response (PRR) at 1 year (186 [69.4%] vs. 134 [50.6%]; OR 2.26; 95% CI 1.58, 3.23; p-value <0.0001) and at 6 months (188 [70.1%] vs. 132 [49.8%]; OR 2.42; 95% CI 1.68, 3.48; p-value <0.0001). A $\geq 50\%$ reduction in UPCR from baseline at any time was achieved by 93.7% of patients in the voclosporin group and 75.2% of patients in the control group. Overall, median times to a 50% reduction in UPCR were 29 days (range 29, 31) and 58 days (range 57, 85), respectively, in the voclosporin and control groups (hazard ratio [HR] 1.96; 95% CI: 1.61, 2.38; $p < 0.0001$); the difference between treatment groups was apparent within the first month of treatment and sustained at 1 year [20,21].
Voclosporin adds to the existing therapeutic options for LN and has potential advantages over other CNIs. The addition of voclosporin to the standard-of-care regimen of MMF/glucocorticoids produced higher response rates and shorter time to CRR. Questions remain to be answered for this regimen, such as the length of treatment, the tapering schedule, and its long-term safety and efficacy for preserving kidney function [21].

The recent EULAR recommendations provide some clarity over the place of biologics in the treatment sequence for lupus. The guideline proposes earlier use of biologics for steroid sparing and suggests that belimumab and anifrolumab can be considered after HCQ without the need to introduce an immunosuppressant first. For LN, the EULAR task force suggests that belimumab and calcineurin inhibitors can be considered at the beginning of the induction treatment for all patients with LN without distinction between class III/IV and V and continued for a minimum of 3 years. Interestingly, voclosporin is not yet approved for use in Europe by the EMA. The ACR guidelines are eagerly awaited to increase the understanding of the role of biologics in the treatment of lupus.

Data is accumulating on the potential of novel therapies to be disease modifiers in lupus. SLE has a waxing and waning disease course—with periods of flare interspersed with periods of low or no clinical disease activity. The result of these episodes of increased disease activity and drug toxicity is progressive organ damage. Based on the framework developed from the definitions of disease modification in other areas, and treatment goals and outcome measures for SLE, including LN, a suggested working definition of SLE disease modification emerged: ‘Disease modification in SLE involves minimizing disease activity with the least treatment-associated toxicities and treatment-associated damage and slowing or preventing organ damage progression (or, in the case of LN, progression to end-stage kidney disease, ESKD)’.

The most definitive criteria are slowing or preventing organ damage progression in SLE as judged by no worsening in the SDI and, in LN, by showing a reduction or no worsening in key surrogates of progression to ESKD, i.e., kidney histopathology and eGFR decline.

Recently, preventing organ damage over >5 years was confirmed for belimumab based on the results of a propensity score-matched comparative analysis of the Toronto Lupus Cohort [22]. A 2023 EULAR abstract evaluated the potential for disease modification for belimumab and proposed that based on the above referenced definition of disease modification, belimumab is a disease modifier in lupus [23]. The framework for disease modification is an important next step in treating to target and in the evaluation of new therapeutics.

**Future treatments & innovative therapeutic strategies**

Among the main contemporary challenges in SLE [24,25] is the need to develop new treatments as well as new therapeutic strategies [26]. Nowadays, drugs of unknown mechanisms of action are no longer being developed and we have largely capitalized on our improved understanding of the immunopathogenesis of SLE to develop more targeted treatments [27].

**Innovative investigational targets**

The Strasbourg group has recently published a systematic review of the 92 investigational drugs in clinical development in SLE, as of August 2022 [28]. Of those, 58 are biological DMARDs (bDMARDs) and 34 are targeted synthetic (ts)DMARDs. Altogether, these drugs were assessed across a total of 203 clinical trials, with 20 candidate drugs having reached phase I, 6 phase Ia/Iib, 51 phase II and 13 phase III. The targeted candidate pathways were very diverse, and mainly comprised inflammatory cytokines and their receptors, intracellular signaling, B cells or plasma cells, co-stimulation molecules, complement fractions, T cells, plasmacytoid dendritic cells, as well as various other immunological targets of interest.

**Drugs targeting B cells**

B cells can be selectively targeted for depletion either via direct surface molecules such as CD19, CD20, and CD22 or indirectly by inhibition of B-cell survival factors such as B lymphocyte stimulator (BlyS), a proliferation-inducing ligand (APRIL), or their receptors (TACI). While randomized trials of the
anti-CD20 antibodies rituximab [29,30] and ocrelizumab [31] failed to show significant benefit in lupus nephritis, obinutuzumab, a humanized type II anti-CD20 monoclonal antibody that induces potent B-cell depletion, has been investigated in a successful phase 2 trial for the treatment of lupus nephritis [32]. Iberdomide, a cereblon modulator which promotes the degradation of the transcription factors Ikaros and Aiolos has been evaluated in a successful phase 2 trial [33], with the SRI-4 at week 24 as the primary end point. The drug has now moved forward to its phase 3 pivotal development plan.

**Drugs targeting co-stimulation molecules**

Almost a dozen investigational drugs target co-stimulation molecules. Dapirolizumab pegol [34], iscalimab, and ruplizumab target the CD40L-CD40 pathway while dazodalibep is a next-generation fusion protein designed to block CD40 ligand (CD40L). Also, the T cell costimulatory molecule CD28 is known to be essential for the activation of pathogenic T cells in autoimmune diseases and three investigational drugs have been assessed against this target: theralizumab, lulizumab pegol, and acazicolcept (also targeting ICOS). Finally, LY3361237 is a first-in-class B- and T-lymphocyte attenuator (BTLA/CD272) agonist.

**Drugs targeting the plasmacytoid dendritic cells (pDCs)**

Plasmacytoid dendritic cells (pDCs) are key players in SLE [27]. Currently, there are two main targeted therapies against pDCs in SLE: Liti limab (BIIB059), an IgG1 monoclonal antibody binding to Blood dendritic cell antigen 2 (BDCA2), a cell-surface receptor [35,36] and daxcilimab (also known as VIB7734), which is an anti-Immunoglobulin-Like Transcript (ILT)-7 monoclonal antibody inducing the depletion of pDCs.

**Drugs targeting TLRs**

Targeting of Toll-Like Receptors (TLRs) 7 & 9 is one of the main mechanisms of action of hydroxychloroquine (HCQ) [37]. Because of the retinal toxicity associated with HCQ use, the identification of alternative drugs with similar mechanisms of action but without ocular toxicity is an important challenge in SLE [25], as the therapeutic alternatives are currently limited to mepacrine, which is not widely available. Investigated agents from this category include DS-7011a, E6742, enpatoran, and afimetoran.

**Targeting other intracellular pathways**

Fifteen molecules targeting the intracellular machinery are currently in clinical development. Among these targets is Bruton’s tyrosine kinase (BTK). Currently, 8 BTKi are investigated in SLE at early stages of development, including Ibrutinib, which is already approved for the treatment of several B-cell malignancies. Of note, the following targeted treatments: evobrutinib (BTKi) [38], lanraplenib (a spleen kinase inhibitor) [39], as well as the 2 JAK inhibitors baricitinib [40,41] and filgotinib [39,42] did not meet their primary end point in some recent phase 2 or 3 trials. However, deucravacitinib, an oral TYK2 inhibitor and upadactinib, a selective JAK1 inhibitor [43] successfully met their phase 2 trial end points and have moved to phase 3 development.

**Drugs targeting other cytokines & chemokines**

The search identified 15 molecules targeting other cytokines, including IL-17, IL23. The results of a multicenter randomized phase 2 studies [44,45] investigating low-dose IL-2 therapy in SLE have been published and larger studies are now needed to confirm these findings.

**Drugs targeting the complement molecules and other targets**

Five molecules targeting the complement molecules or pathways, including ravulizumab (anti-C5), pegcetacoplan (anti-C3), iptacoplan (anti-complement factor B), and vemircopan (anti-complement factor D), are investigated in SLE. Ten other investigational drugs with various mechanisms of action (targeting CD30, IgE, MASP-2, or the S1PR1, etc ...) are also investigated. Novel strategies which target platelet activation are also being investigated in SLE [46].
Innovative therapeutic strategies

While the identification of new targets and subsequently is much needed, researchers are actively engaged in the development of new therapeutic strategies for IMIDs [28], including the use of mAbs in combination [47], of bispecific monoclonal antibodies, nanobodies and nanoparticles, therapeutic vaccines, siRNA interference, autologous hematopoietic stem-cell transplantation (aHSCT) and Chimeric Antigens Receptor (CAR)-T cells. While most of these novel therapeutic strategies are still being evaluated, they offer the promise of future improvements for the care of lupus patients.

Combination of targeted therapies

There is strong evidence from other medical fields such as oncology and hematology, that combination therapies might be effective in selected patients. Similarly, two or more non-redundant pathways could be targeted concomitantly or in sequence in SLE. The serum increase of B-cell activating factor (BAFF) after rituximab-induced B-cell depletion has led to trials combining in systemic lupus erythematosus (SLE) [47]. In a phase 2 trial [47], belimumab after rituximab significantly reduced serum IgG anti-dsDNA antibody levels and reduced risk for severe flare in patients with SLE that was refractory to conventional therapy. Conversely, results from a phase 3 trial [48] have been presented at the ACR Convergence 2021, and suggest that adding a single cycle of rituximab to belimumab therapy does not significantly improve disease control in SLE.

Bispecific antibodies & nanobodies

Bispecific antibodies (BsAbs) have the ability to target different pathophysiological pathways simultaneously, which may lead to more effective treatments. While most bispecific are currently in the early stages of clinical development, they may soon supplant the classical monoclonal antibodies. In SLE, 5 BsAbs characterized by various mechanisms of action are currently assessed. Tilibulizumab is a BsAb that is composed of two divalent antibodies that act independently and target both BAFF and IL-17A. AMG570 targets the inducible T-cell costimulator ligand (ICOSL) and BAFF [49]. bsHexAb targets CD20 and CD22 [50]. Obexelimab (XmAb5871) is a humanized Fc-engineered antibody that binds to CD19 on the B-cell surface and MT-6194 is a bispecific antibody that targets both IL-17A and IL-6R. With the same advantages as bispecific antibodies but also additional advantages in terms of production, structure, solubility and resistance to pH and temperature ranges, nanobodies, which are made from heavy-chain antibodies that occur naturally in camelids and sharks, are likely going to be one of the big next steps in the targeted treatment of IMIDs.

Autologous hematopoietic stem-cell transplantation

The rationale for autologous hematopoietic stem-cell transplantation (aHSCT) in autoimmune diseases relies on the ablation ability of the self-reactive immune cells using chemotherapy or total body irradiation followed by generation of a new self-tolerant immune system, from autologous hematopoietic stem cells. This procedure has the potential to alter the course of autoimmune diseases by resetting the immune system and establishing a new immune repertoire with restored immune checkpoints. In SLE, aHSCT appeared effective and safe in a recent case series of 22 patients with LN refractory to immunosuppressive therapy. While no patient died during the follow-up, the 10-year disease-free survival rate was 35% and only 10% of patients required kidney support after 10 years [51]. Also [52][52] [52][51], 5 of 8 patients with refractory SLE [52] achieved a complete response, but two patients with nephritis and underlying comorbidities had early death from infection and multi-organ failure. Given the risk associated with the procedure itself, this “immune reset procedure” is currently only conceivable in the most severe cases with the engagement of the vital prognosis [53]. The optimization of conditioning procedures and the possible use of HSCT in addition to other strategies makes it a non-negligible alternative in the near future for our most refractory patients.

Chimeric antigen receptor (CAR) T cells

Chimeric antigen receptor (CAR) T cells are an engineered cellular product that combines B-cell antibody-based antigen recognition with T-cell cytotoxicity. In the context of IMIDs, some promising results are shown with cytotoxic CD8+ CD19 CAR-T cells designed to deplete the B-cell population [54].
Compared to monoclonal antibodies, CAR-T cells may have several advantages as they are long-lived cells that can multiply, can traffic to the lymphoid tissues or target organs and develop into memory populations that can prevent the re-emergence of pathogenic lymphocytes. In SLE, some promising results were shown with CD19-targeted CAR-T cell therapy in severe refractory diseases. A small series of five patients, refractory to several immunosuppressive treatments, achieved SLE remission 3 months after the CD19 CAR-T cell administration without any toxicity signal [55] and this was presented as an updated abstract about seven patients at EULAR 2023.

**Therapeutic vaccination**

Another interesting therapeutic approach targeting pro-inflammatory cytokines is the use of vaccines to create an endogenous natural immune response against those cytokines. Using this technology, a Kinoid interferon alpha® (K-IFNα) was synthesized using inactivated IFN-α-2b to generate polyclonal neutralizing antibodies targeting this cytokine. K-IFNα® was assessed in a phase IIb study of patients with active SLE and positive IFNGS despite standard of care [56]. The coprimary end points were not met, although more patients attained a lupus low disease activity state (LLDAS) with a significant glucocorticoid sparing effect of K-IFNα® over the placebo.

**RNA interference**

Mammalian cells express many small RNA sequences, called microRNA (miRNA) to fine-tune the expression of genes at a post-translational level. Synthetic interfering RNA named siRNA was later constructed and showed efficacy in inducing mRNA degradation or silencing, opening the door to therapeutic interventions. In lupus-prone mice, targeting hypoxia-induced factor 1α, resulted in decreased autoantibodies levels and improved kidney [57]. Also, siRNA targeting of either BLyS or of the interferon regulatory factor 5 resulted in an improvement in lupus-prone mice [58].

**Conclusion**

The therapeutic management and prognosis of SLE have profoundly evolved with changes in the therapeutic armamentarium [59]. With the broad pipeline of targeted treatments in clinical development, current challenges are transitioning from the availability of new drugs to the selection of the most adequate drug (or drug combination) at the patient level. Among the most promising future evolutions in the therapeutic strategies for lupus are the use of combination of biologics, nanobodies, aHSCT, and CAR-T cells, while other advanced technologies such as RNA interference, remain at a more preliminary stage of development. Altogether, this further increases the need to better characterize immune pathways at the patient level, as a way to enable tomorrow’s fully precise and patient-tailored lupus medicine.

**Practice points**

- New targeted drugs have been actively investigated for SLE
- New drugs and extended indications include anifrolumab, voclosporin, and belimumab
- More than 90 investigational drugs are currently in clinical development in SLE
- Selecting the most adequate strategy at the patient level is a major challenge

**Research agenda**

- Biomarkers are needed to predict treatment response at the patient level and enable full precision medicine in SLE.
- Placebo-controlled clinical trials are needed in which the efficacy and safety of new therapeutic strategies in SLE are studied.
Author contributions

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