# Advances in the management of systemic lupus erythematosus

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

## Abstract

Systemic lupus erythematosus (SLE) is a severe multisystem autoimmune disease that can cause injury in almost every body system. While considered a classic example of autoimmunity, it is still relatively poorly understood. Treatment with immunosuppressive agents is challenging, as many agents are relatively non-specific, and the underlying disease is characterized by unpredictable flares and remissions. This State of The Art Review provides a comprehensive current summary of systemic lupus erythematosus based on recent literature. In basic and translational science, this summary includes the current state of genetics, epigenetics, differences by ancestry, and updates about the molecular and immunological pathogenesis of systemic lupus erythematosus. In clinical science, the summary includes updates in diagnosis and classification, clinical features and subphenotypes, and current guidelines and strategies for treatment. The paper also provides a comprehensive review of the large number of recent clinical trials in systemic lupus erythematosus. Current knowns and unknowns are presented, and potential directions for the future are suggested. Improved knowledge of immunological pathogenesis and the molecular differences that exist between patients should help to personalize treatment, minimize side effects, and achieve better outcomes in this difficult disease.

## Introduction

Most clinicians learnt at medical school that systemic lupus erythematosus (SLE, or lupus) is the archetypal multisystem autoimmune disease. Patients classified as having systemic lupus erythematosus manifest immune mediated inflammatory injury in virtually every organ system, and therefore, lupus can present across all fields of medicine. This well known clinical heterogeneity results in many difficulties, including how to make the diagnosis or standardize treatment approaches. We now also know that patients clinically classified as having systemic lupus erythematosus represent a cluster of differing molecular pathologies that could explain these diverse phenotypes. The challenges posed by the combination of clinical and biological heterogeneity have contributed to a paucity of major breakthroughs in the treatment of systemic lupus erythematosus. Even though recent years have seen the approval of three new treatments for systemic lupus erythematosus and lupus nephritis, the management of most patients has changed little since the last century, with long term outcomes characterized by high morbidity and mortality. This stagnation is in stark contrast to other autoimmune diseases such as rheumatoid arthritis, where the adoption of treat-to-target strategies and the use of targeted treatments have resulted in paradigm changes in patient outcomes. Moreover, challenges in the measurement of treatment response continue to contribute to trial failures, and the endpoints used in trials are neither used routinely in clinical practice nor reflected in management guidelines. Clearly, much remains to be done to improve the lives of patients with systemic lupus erythematosus.

This review summarizes the latest approaches in the management of systemic lupus erythematosus, focusing on independently confirmed evidence, for example, in independent clinical or laboratory studies. Despite some areas being underpinned by robust evidence, major gaps in knowledge remain. We suggest objectives for future research to bridge these gaps and improve the lives and life expectancy of patients with systemic lupus erythematosus.

## Epidemiology of systemic lupus erythematosus

The incidence and prevalence of systemic lupus erythematosus vary widely between global regions. The differences in epidemiological estimates in world populations are likely due to differences in access to care in different regions, environmental exposures and socioeconomic status, genetic risk factors, and heterogeneity in features of systemic

lupus erythematosus,[1] although differences in methodology between studies could also contribute. Nevertheless, the consensus is that systemic lupus erythematosus disproportionately affects women, with a female to male ratio of about 9:1, and certain populations, including African Americans, Amerindians, and Asians.[1 2]

In the United States, the overall prevalence of systemic lupus erythematosus was estimated to be 72.8 per 100 000, with an overall incidence of 5.1 per 100 000 person years from 2002 to2009.[2 3] An upward trend in both incidence and prevalence of systemic lupus erythematosus was recently identified in a US population study in Minnesota, in which the prevalence of systemic lupus erythematosus increased from 30.6 per 100 000 in 1985 to 97.4 in 2015, with a 2% annual increase in incidence over 43 years (1976-2018).[4] This increase could relate to increased recognition. Similar patterns of increased prevalence of systemic lupus erythematosus over time have also been identified in other geographic regions, including Europe and Asia.[1 5 6]

### Sources and selection criteria

We searched PubMed and Medline for publications on systemic lupus erythematosus from 2010 to2022 in two parallel search strategies. For clinical studies, we used the search term "lupus" and the filters "clinical study", "clinical trial", and "randomized controlled trial", yielding 1238 reports. Case reports, purely descriptive studies, uncontrolled trials, and studies with few participants were excluded. For studies of pathogenesis, we used the search terms "systemic lupus erythematosus" AND "human" AND "English" AND "molecular pathogenesis" NOT "review", which returned 1272 results. Studies that were exclusively in vitro or in experimental animals, or with findings of limited reproducibility within the report or between reports, were excluded. Clinical studies that were prioritized included large double blind randomized controlled trials (including both lupus and lupus nephritis trials), those with large numbers of subjects or comprehensive scope, and for basic and translational science, we prioritized those with robust or replicated supporting data, or multiple parallel lines of evidence supporting the conclusions.

### Classification and diagnosis

The diagnosis of systemic lupus erythematosus remains a clinical one.[7] However, the use of classification criteria has been widely adopted for research purposes, enabling consistency between studies. Classification criteria for systemic lupus erythematosus have latterly evolved from the widely used American College of Rheumatology criteria that were last updated in 1997,[8] and a competing classification system produced by an international group of expert clinicians, the systemic lupus international collaborating clinics (SLICC), intended to increase sensitivity while retaining specificity.[9] Both sets of criteria determine if the number of defined manifestations exceeds a threshold, which would be a testament to the implicit assumption of multisystem involvement in systemic lupus erythematosus. Recently, a joint effort between the American College of Rheumatology and the European Alliance of Associations for Rheumatology (EULAR) produced new classification criteria,[10] centered around an entry requirement for a positive antinuclear antibody test and scored using weighted domains for various clinical and laboratory findings. The sensitivity of these criteria is reflective of the SLICC criteria, while retaining the specificity of the earlier American College of Rheumatology criteria.

Classification criteria have been used in virtually all studies discussed in this review. Importantly though, unlike malignant or infectious diseases where a causal mutation or microorganism is implicit to the diagnosis, classification of a patient as having systemic lupus erythematosus does not imply a specific causal pathology. The pooling of clinically dissimilar cases under a single diagnostic rubric reinforces the concept that systemic lupus erythematosus is heterogeneous, in a sort of taxonomic vicious cycle. As outlined in subsequent sections, evidence is mounting for considerable biological heterogeneity among patients classified clinically as having systemic lupus erythematosus, posing the possibility that classifying dissimilar pathologies under a single umbrella term is an error.[11] This possibility complicates all research in the lupus field, from clinical measurement and trials through to genetic and biological analysis.

### Pathogenesis of systemic lupus erythematosus: susceptibility

Knowledge of the pathogenesis of systemic lupus erythematosus has advanced considerably in the past two decades, accelerated by a move towards studying human systemic lupus erythematosus instead of murine models, and technologies allowing studies of gene sequencing and gene expression in large cohorts. We consider certain aspects of pathogenesis to now represent settled science, while many unanswered questions remain (table 1).

#### Genetics

Systemic lupus erythematosus is characterized by a strong familial concordance, including greater concordance in monozygotic twins than dizygotic twins (24-56% in monozygotic *v* 2-4% in dizygotic[12 13]), and a risk in first degree relatives similar to that of dizygotic twins. The pattern of inheritance generally fits that of a genetically complex disease with multiple moderate risk factors.[14 15] Recent genome wide association scans have supported this idea, with many genetic risk loci identified with odds ratios for disease between 1.2 and 1.7, and some that fall above or below this range.[15-17] The HLA region is the strongest common risk factor for systemic lupus erythematosus, including alleles of HLA-DR. A recent study identified that the HLA class II genetic association appears to

be strongest among patients with systemic lupus erythematosus possessing the type 1 interferon signature[18] (see below), and other studies have also suggested that the common systemic lupus erythematosus risk alleles could be specifically associated with this patient subgroup.[19]

Single gene mutations of large effect can also cause systemic lupus erythematosus. Recessive C1q deficiency has long been known as a monogenic cause of systemic lupus erythematosus, and several other monogenic causes have been discovered, such as mutations in DNAse1L3, TREX1, and TLR7.[20 21] In general, these mutations are in genes that function in the immune system or DNA processing, consistent with our concept of systemic lupus erythematosus as an autoimmune disease with an antinucleic acid response. These monogenic variants are each very rare, and even if many more are discovered it seems that only a small percentage of systemic lupus erythematosus will be attributable to monogenic causes. A greater proportion of monogenic versus polygenic systemic lupus erythematosus is present in childhood onset disease,[20] as might be expected, and polygenic childhood systemic lupus erythematosus is associated with more known common risk variants.[22 23]

Despite advances in our understanding of the genetic risk factors underlying systemic lupus erythematosus, much of the heritability remains unexplained. Additive genetic models still do not account for the majority of the heritability of systemic lupus erythematosus,[24] and gene-gene and gene-environment interactions (see below) probably contribute (it being unlikely that all genetic risk factors work in complete isolation). For example, a recent paper showed that Epstein Barr virus proteins occupy approximately 50% of the promoter regions of common risk loci for systemic lupus erythematosus in B cells, suggesting that Epstein Barr virus modulates the impact of these alleles.[25] This possibility is intriguing, given epidemiological data supporting Epstein Barr virus as a causal factor in systemic lupus erythematosus.[26]

While over 91 gene loci have been implicated as common risk factors in systemic lupus erythematosus,[27] we still do not know the function of most of them. Studies have suggested, for example, that the protein tyrosine phosphatase non-receptor type 22 (PTPN22) variant alters lymphocyte function in complex ways.[28] Risk loci for the type I interferon pathway appear to confer gain of function in that pathway[29]; a recent study suggested that some risk loci for interferon pathway systemic lupus erythematosus are protective against death from acute covid-19.[30] These data support the idea that genetic risk factors for autoimmune disease have endured owing to positive selection pressure relating to effects on immunity against pathogens.[30] Functional studies of the known risk loci for systemic lupus erythematosus could provide pathological insight, as well as new targets for treatment.

### Ancestry

While genetic studies have assessed multiple populations, non-European ancestry populations are less well studied, and thus less is known about their genetic susceptibility to systemic lupus erythematosus. The HLA region encodes multiple genes essential to immune function,[31] and has been most strongly associated with risk of systemic lupus erythematosus in European and Chinese populations. The HLA region is also associated with systemic lupus erythematosus in Amerindian and African American populations, but with a different pattern of association and different alleles implicated. For example, a recent fine mapping of the HLA region in 1494 African American systemic lupus

**Table 1 | Summary of settled science and unanswered questions in pathogenesis of systemic lupus erythematosus**

| Settled science | Evidence | Unanswered questions |
|---|---|---|
| Role of innate immunity/type 1 interferon | Incredibly reproducible interferon signature in blood, tissues<br>Positive phase 3 trials, resulting in regulatory approval | Cellular source(s) of interferon are not clear<br>Stimulus of innate immunity:<br>many different nucleic acid types and sources seem possible, including nucleic acid immune complexes, nucleic acid sensors; sources could include apoptotic debris, NETs from NETosis, viruses, etc. |
| Role of humoral immunity | Prominence of autoantibodies in patients led to use in diagnostic criteria (although now that could be seen as self-fulfilling)<br>Efficacy of belimumab in systemic lupus erythematosus and nephritis | Why do so many people have antinuclear antibody but not a disease?<br>What are the pathological consequences of different autoantibody specificities<br>(eg Sm, Ro), are they involved in pathogenesis or simply markers of disease? |
| Ancestral variation in clinical phenotype | Clear evidence across multiple studies that patients of non-European ancestry with systemic lupus erythematosus are both more frequently and more severely affected | The underlying biological and environmental factors are not well understood, and differences between populations are likely due to a combination of factors |
| Sex prevalence (9:1 female to male ratio) | Clear female sex skewing which is more prominent in reproductive years<br>Additional X chromosome in Klinefelter syndrome increases risk of lupus | Despite the large sex differential in disease, the biological basis is incompletely understood<br>Not enough X chromosome risk factors that could explain the data on Klinefelter syndrome |
| Genetics | Familial predilection to systemic lupus erythematosus and other autoimmune diseases<br>Well validated risk loci (both HLA and non-HLA) | Function of risk genes in the immune system (and other organ systems) is largely unknown, gene-gene and gene-environment interactions probably exist but have been difficult to identify |
| Epigenetics | Epigenetic programs can be detected in patients, such as the interferon signature | Whether these epigenetic events occur before or after disease onset is not clear |

NET=neutrophil extracellular trap.

erythematosus cases and 5908 controls revealed relatively short range linkage disequilibrium with a strong, narrow signal at the HLA class II region. The most significantly associated HLA haplotypes in European ancestry and African ancestry participants were HLA-DQB*02:01 and HLA-DRB1*15:03, respectively.[32]

While some genetic risk factors appear to be common across populations, clear examples of ancestry specific associations exist as well. It seems likely that these differences reflect functional variation in immune genes in ancestral populations caused by infectious evolutionary pressures. One such example is the APOL1 gene. Two coding change variants APOL1 identified exclusively in sub-Saharan African genomes are thought to have been evolutionarily conserved by conferring protection against *Trypanosoma brucei*, the parasite that causes African trypanosomiasis.[33] However, the APOL1 high risk genotype is associated with risk of end stage kidney disease in patients with lupus nephritis, as well as several other adverse renal phenotypes.[34 35] Correspondingly, a missense polymorphism in PTPN22 is highly associated with autoimmune conditions, including systemic lupus erythematosus in European ancestry, but not clearly in African-American or Asian-American populations.[36] Variants in the promoter region of the IRF5 gene have been associated with systemic lupus erythematosus across populations, but a separate, Neanderthal derived haplotype is also prevalent in populations with Neanderthal admixture.[37 38] These data highlight the importance of inclusivity in genetic research in systemic lupus erythematosus.

### Sex bias in systemic lupus erythematosus

Although the biological basis of the 9:1 female to male ratio of systemic lupus erythematosus incidence remains largely unexplained, accumulating evidence implicates the X chromosome. Patients with an extra X chromosome, such as those with Klinefelter syndrome (47,XXY)[39] and trisomy X syndrome (47,XXX),[40] have a higher prevalence of systemic lupus erythematosus. Men with Klinefelter syndrome are estimated to have a 14-fold higher risk of systemic lupus erythematosus than karyotypically normal men (46,XY),[39] whereas women with trisomy X syndrome have a prevalence of systemic lupus erythematosus that is about 2.5 times higher than in karyotypically normal women (46,XX),[40] an effect that seems to be largely independent of circulating sex hormones. Furthermore, many genes that regulate the immune response are located on the X chromosome, several of which escape X chromosome inactivation[41] or can be demethylated and expressed in the inactive X chromosome. These include genes that directly regulate the innate and adaptive immune responses such as IRAK1, CD40LG, TLR7, BTK, and CXorf21/TASL.[42-48] This process has been shown to be dynamic in human B cell lineages.[49] Taken together, these findings support the concept of a gene-dose effect from the X chromosome as a contributor to systemic lupus erythematosus susceptibility. However, the relative contribution of, and exact mechanisms by which, gene overexpression due to escape from X chromosome inactivation leads to autoimmunity remain poorly understood. Although not yet directly shown to be subject to aberrant inactivation, the gene TSC22D3, encoding the glucocorticoid induced leucine zipper (GILZ) protein, is also located on the X chromosome[50]; GILZ deficiency results in spontaneous B cell hyperactivation and a lupus-like phenotype in mice,[51] while GILZ also restrains Th17 and type I interferon pathways.[52-54]

Sex hormones having a role in sexual dimorphism in systemic lupus erythematosus is supported by the more prominent female to male ratio in patients during their reproductive years, increased flares in high estrogen settings such as pregnancy, and higher risk of developing systemic lupus erythematosus in postmenopausal women after estrogen administration.[55 56] In addition, estrogens have been shown to accelerate or worsen disease in murine models of lupus[57 58] and have several immunomodulatory effects.[59] Estrogens have been shown to upregulate Bcl-2 and anti-B cell activating factor (BAFF) and potentiate the survival, activation, and differentiation of B cells into antibody producing cells.[60-64] Estrogens have been shown to increase type I interferon induced gene expression in human cells in vitro, and exert a number of proinflammatory activities on the innate immune system.[65 66] Estrogens can also modulate the immune response via epigenetic modifications, inducing changes in DNA methylation patterns and regulating the expression of microRNAs.[67-69] Overall, it seems likely that the strong female skewing in systemic lupus erythematosus represents the convergence of multiple genetic, epigenetic, hormonal, and environmental factors. Importantly from a clinical perspective, a prospective placebo controlled study of 183 patients showed that oral contraception containing estrogen does not exacerbate systemic lupus erythematosus.[70]

### Epigenetics and systemic lupus erythematosus

Epigenetics, or the sum of genome wide chromatin modifications that do not change DNA sequences, includes DNA methylation, histone modification, microRNA regulation, and 2D chromatin interactions, all of which can alter chromatin accessibility and transcription factor binding.[69 70] Importantly, both genetic and environmental factors—particularly during early development—can influence epigenetic modifications, therefore, the epigenome can mediate disease associated gene-environment interactions.[71] This relatively new area of research could help to explain how environmental factors affect systemic lupus erythematosus risk.

The most robustly studied epigenetic modification in rheumatic diseases is DNA methylation, a process by which genomic cytosine nucleotides positioned near adjacent guanine nucleotides (CpG sites) are methylated by DNA methyltransferases.[72] Multiple

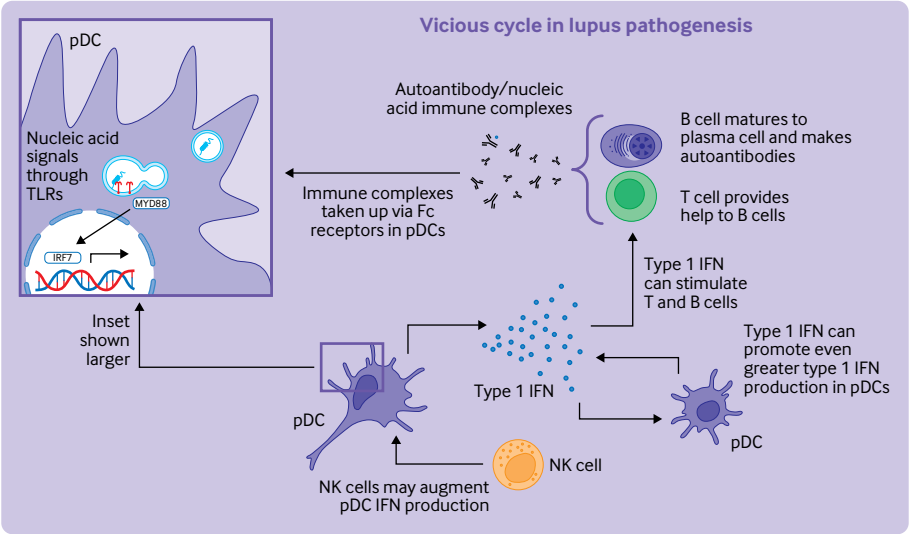


**Fig 1 | Cellular and molecular pathogenesis in systemic lupus erythematosus. The molecular events in lupus can be represented in the form of a cycle, in which innate immune stimuli, such as nucleic acid immune complexes, stimulate cytokine responses, which then stimulate T and B cells of the adaptive immune response, producing autoantibodies that can bind nucleic acids. Evidence to date supports this cycle, but the starting point is not currently clear. IFN=interferon; IRF7=interferon regulatory factor 7; MYD88=myeloid differentiation primary response 88; NK=natural killer; pDC=plasmacytoid dendritic cell; TLR=toll-like receptor**

epigenetic studies in systemic lupus erythematosus document methylation profiles associated with systemic lupus erythematosus and specific systemic lupus erythematosus organ involvement, including nephritis.[73 74] In cluster analysis, differentially methylated CpG sites have been shown to distinguish three systemic lupus erythematosus endophenotypes; with the milder cluster characterized by hypermethylation of interferon alfa responsive loci, compared with the two more severe clusters.[74] These data are consistent with the finding that systemic lupus erythematosus is more severe in patients with the transcriptional interferon signature.[75 76] The bulk of these CpG sites remained stable over two years, suggesting that epigenetic profile could be a prognostic biomarker for newly diagnosed patients.[77] Larger, longitudinal cohorts will be necessary to further understand how disease activity and treatments could affect the dynamic methylation profile in systemic lupus erythematosus. Importantly, because differentially methylated CpG sites differ between immune cell types, methylation studies also need to compare specific cellular compartments. Epigenetic modifications specific to cell type might provide clues for both risk stratification and personalized medicine.

## Pathogenesis of systemic lupus erythematosus: pathways

### Humoral autoimmunity

Autoantibodies are a cardinal feature of systemic lupus erythematosus, and their presence in the circulation forms part of the basis for the initial diagnosis, formal classification, and ongoing monitoring of disease activity. The antinuclear antibody test is positive in most patients with systemic lupus erythematosus, and typically remains positive for the patient's lifetime; this is reflected by the fact that a positive antinuclear antibody test is required for classification as systemic lupus erythematosus under the latest criteria.[10] While antinuclear antibody is useful as a screening test, many other conditions are associated with a positive antinuclear antibody, including acute and chronic viral infections, cancer, and many other autoimmune diseases. The rate of a positive antinuclear antibody test in the general population is estimated at 12-16%, with rates that are almost double that in people over 70,[78] vastly exceeding the prevalence of systemic lupus erythematosus. While some studies have suggested that a positive antinuclear antibody test is associated with increased mortality in the general healthy population,[79] these results have not always been confirmed, and it does not appear that antinuclear antibodies as assessed by screening test indicate a pathological state.[78] Specific autoantibodies associated with systemic lupus erythematosus that are tested in the clinical setting, such as anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, and anti-La, are not frequently found in healthy individuals. These autoantibodies are, therefore, useful follow-up tests for the assessment of systemic lupus erythematosus, and might be more directly pathogenic. Immune complexes formed by these autoantibodies specific to systemic lupus erythematosus can induce type I interferon production in innate immune cells when taken up via Fc receptors into the endosome.[80] Interestingly, these same autoantibodies can be observed in circulation many years before the diagnosis of systemic lupus erythematosus,[81] and are accompanied by some of the characteristic cytokine dysregulation observed in systemic lupus erythematosus, such as high levels of interferons.[82]

**Table 2 | Trials of novel treatments for systemic lupus erythematosus and lupus nephritis. Products highlighted in green have received regulatory approval for use in systemic lupus erythematosus or lupus nephritis**

| Agent (target) | Inclusion criteria | No of patients | Primary outcome measure | Result* | Reference |
|---|---|---|---|---|---|
| DHEA/prasterone (sex hormones) | SLAM score >7 | 120 | Mean change from baseline in SLAM score | DHEA -2.6 +/- 3.4; PBO 2.0 +/- 3.8 | 117 |
| | Severe active lupus | 21 | Quantitatively specified improvement of the principal severe lupus manifestation | DHEA 7/9 patients versus PBO 4/10 patients (P< 0.10) | 118 |
| | SLAM score >7 or SLEDAI >2 | 381 | no clinical deterioration + improvement or stabilization in two disease activity measures (SLEDAI†, SLAM) and 2 quality of life measures (PtGA and Krupp Fatigue Severity Scale). | DHEA 51.3%; PBO 42.2% (P=0.074). | 119 |
| Rituximab (CD20) | >1 BILAG A or >2 BILAG B score | 257 | Major clinical response (BILAG C scores or better in all organs without severe flare) | Rituximab 15.9%, PBO 12.4%; P=0.97[5] | 120 |
| Abatacept (CD28, via CTLA4) | BILAG defined active polyarthritis discoid lesions or pleuritis/pericarditis | 118 | Proportion of patients with a new BILAG defined flare | Abatacept 79.7%, PBO 82.5%; (treatment difference −3.5 (95% CI 15.3 to 8.3) | 121 |
| Belimumab (BAFF) | SLEDAI >4 | 449 | Per cent change in SELENA–SLEDAI score and time to first mild/moderate or severe flare | Belimumab −19.5% + 2.7 versus PBO: −17.2% + 5[-1] | [1]22 |
| | SLEDAI >6 and seropositive | 867 | SRI(4)‡ | Belimumab 58%, PBO 44%, odds ratio 1.83 (1.30 to 2.59), P=0·0006. | 123 |
| | SLEDAI >6 and seropositive | 819 | SRI(4) | Belimumab 43.2% versus PBO 33.5%; P=0.017 | 124 |
| Edratide (hCDR1) | SLEDAI 6-12 | 340 | Reduction in SLEDAI 2K and adjusted mean SLEDAI 2K | No difference between treatment arms (numerical results not reported) | 125 |
| Epratuzumab (CD22) | >1 BILAG A or >2 BILAG B and SLEDAI >6 | 227 | BICLA | PBO 21% versus epratuzumab 200 mg/mo (30.8%), 800 mg/mo (26.3%), 2400 mg/mo 43.2%; P=0.148. | 126 |
| | >1 BILAG A or >2 BILAG B and SLEDAI K >6 and seropositive | 793 | BICLA | PBO 34.1%, 1200 mg every other week 39.8% (P=0.175 versus placebo), and epratuzumab 600 mg every week 37.5% (P=0.442) | [12]7 |
| | >1 BILAG A or >2 BILAG B and SLEDAI K >6 and seropositive | 791 | BICLA | PBO 33.5%, 1200 mg every other week 34.1% (P=0.899 versus placebo), and epratuzumab 600 mg every week 35.2% (P=0.716) | 127 |
| Tabalumab (BAFF) | SLEDAI >6 and seropositive | 1164 | SRI(5) | PBO 29.3%, 120 mg Q2W 31.8% and 120 mg Q4W 35.2% (P>0.05) | 128 |
| | SLEDAI >6 and seropositive | 1124 | SRI(5) | PBO 27.7%, 120 mg Q2W 38.4% (=0.002), 120 mg Q4W 34.8% (p=0.051) | [12]9 |
| Atacicept (BAFF/APRIL) | SLEDAI >6 and seropositive | 306 | SRI(4) | PBO 44.0%, atacicept 75 mg 57.8% (adjusted odds ratio 1.78; 95% CI 1.01 to 3.12), P=0.045, atacicept 150 mg 53.8% (adjusted odds ratio 1.56; 95% CI 0.89 to 2.72), P=0.121 | 130 |
| Blisibimod (BAFF) | SLEDAI >6 and seropositive | 547 | SRI(5) | PBO 35.3%, blisibimod 37.2%, P=0.635 | 131 |
| | SLEDAI >10 and seropositive | 442 | SRI(6) | PBO 42.3%, blisibimod 46.9%, P=0.35[2] | [13]2 |
| Rontalizumab (interferon alfa) | >1 BILAG A or >2 BILAG B and seropositive | 238 | Reduction in all BILAG A to B or less, and/or B to C or less | PBO 41.8%, rontalizumab 45.5%, P=0.60 | 133 |
| Sifalimumab (interferon alfa) | SLEDAI >6 and >1 BILAG A or >2 BILAG B and PGA >1 and seropositive | 432 | | PBO 45.4%, sifaljmumab 200 mg 58.3% (P=0.057), 600 mg 56.5% (P=0.094), 1200 mg 59.8% (P=0.0[31]) | 134 |
| Anifrolumab (IFNAR) | SLEDAI >6 plus BILAG >1A or >2B plus PGA >1 and seropositive | 307 | SRI(4) plus glucocorticoid taper | PBO 17.6%, anifrolumab 300 mg 34.3%, odds ratio 2.38 (1.33–4.26), P=0.014; anifrolumab 1000 mg 28.8%, odds ratio 1.94 (1.08–3.49), P=0.0[63] | [1]35 |
| | SLEDAI >6 plus BILAG >1A or >2B plus PGA >1 and seropositive | 457 | SRI(4) | PBO 40%, anifrolumab 300 mg 36%; difference −4.2 (95% CI −14.2 to 5.8), P=0·41 | 113 |
| | SLEDAI >6 plus BILAG >1A or >2B plus PGA >1 and seropositive | 362 | BICLA | PBO 31.5%, anifrolumab 300 mg 47.8%, adjusted difference 16.3 (6.3 to 26.3); P=0.001 | 112 |

(*Continued*)

**Table 2 | Continued**

| Agent (target) | Inclusion criteria | No of patients | Primary outcome measure | Result* | Reference |
|---|---|---|---|---|---|
| Evobrutinib (BTK) | SLEDAI ›6 and seropositive | 469 | SRI(4) | PBO, 45.6%; evobrutinib 25 mg 55.7% (difference 10.0, odds ratio 1.55 (0.91-2.64), P=0.052); 75 mg 51.7% (difference 6.1, odds ratio 1.29 (0.76-2.18), P=0.1741; 100 mg 48.2%, difference 2.6, odds ratio 1.13 (0.67-1.93), P=0.329) | 136 |
| Fenebrutinib (BTK) | SLEDAI ›8 plus PGA ›1 and seropositive | 260 | SRI(4) | PBO 44%, fenebrutinib 51%, (P=0.37) | 137 |
| Dapirolizumab (CD40) | SLEDAI ›6 plus BILAG ›1A or ›2B and seropositive | 182 | BICLA dose-response association | P=0.07 | 138 |
| Filgotinib (JAK1) and lanraplenib (SYK)§ | CLASI A score ›10 | 47 | Least squares mean change in CLASI A score | PBO −5.5 (standard error 2.56), filgotinib −8.7 (1.85), lanraplenib 4.5 (1.91) | 139 |
| Ustekinumab (interleukin 12/23) | SLEDAI ›6 and seropositive | 102 | SRI(4) | PBO 33%, ustekinumab 62%, difference 28% (10–47), P=0.006 | 140 |
| | SLEDAI ›6 and seropositive | 516 | SRI(4) | PBO 56%, ustekinumab 4 4% | 141 |
| Baricitinib (JAK1/2) | SLEDAI ›6 and seropositive | 760 | SRI(4) | PBO 46%, baricitinib 4 mg 57% odds ratio 1.57 (1.09-2.27), P=0.016 | 142 |
| | SLEDAI ›6 and seropositive | 775 | SRI(4) | PBO 46%, baricitinib 4 mg 47% odds ratio 1.07 (0.75-1.53), P=0.71 | 143 |
| Litifilimab (BDCA2) | ›4 tender joints and ›4 swollen joints and SLEDAI skin domain positive and seropositive | 132 | Change from baseline in the sum of the swollen and tender joint counts | Least-squares mean (± standard error) change from baseline PBO 11.6±1.3, litifilimab 15.0±1.2, difference −3.4 joints (−6.7 to −0.2) P=0.04) | 144 |
| | | 132 | Per cent change in CLASI A | Least squares mean (± standard error) per cent changes in CLASI A PBO −14.5±6.4, litifilimab 50 mg −38.8±7.5 150mg −47.9±7.5, 450 mg −42.5±5.5 | 145 |
| Iberdomide (Cereblon-Ailois/ Ikaros) | SLEDAI ›6 and seropositive | 289 | SRI(4) | PBO 35%, iberdomide 0.45mg 54%, adjusted difference, 19.4 (4.1 to 33.4); P=0.01) | 146 |
| Deucravicitinib (TYK2) | SLEDAI ›6 plus BILAG ›1A or ›2B and seropositive | 363 | SRI(4) | PBO 34.4%; deucravicitinib 3 mg BD 58.2% (odds ratio 2.8 (1.5-5.1, P‹0.001); 6 mg BID 49.5% (odds ratio 1.9 (1.0-3.4, P=0.02); 12 mg daily 44.9%. | 147 |
| Abetimus (anti-dsDNA) | Renal flare within the past 4 years | 298 | Renal flare | PBO 89 months, abetimus 124 months | 148 |
| Rituximab (CD20) | Active lupus nephritis on biopsy within 12 months, and UPCR ›1.0 | 144 | Complete renal response (inactive urinary sediment and UPCR ‹0.5, normal or improved serum creatinine) | PBO 30.6%, rituximab 26.4% | 149 |
| Abatacept (CD28, via CTLA4) | Active lupus nephritis class III or IV on biopsy within 12 months; if ›3 months, also UPCR ›0.44 and active sediment | 298 | Confirmed complete response (UPCR ‹0.26, inactive sediment, no loss of eGFR) | PBO 20.0%, abatacept high dose 22.2%, abatacept lower dose 27.3%, | 150 |
| Belimumab (BAFF) | Active lupus nephritis class III, IV, or V on biopsy within 6 months, UPCR ›1.0, and eGFR ›30 mL/min/1.73m2 | 448 | Primary efficacy renal response (UPCR ‹0.7, eGFR within 20% of baseline, or ›60 mL/min/1.73m2) | PBO 32%, belimumab 43%, odds ratio 1.6 (1.0 to 2.3), P=0.03 | 151 |
| Voclosporin (Calcineurin) | Active lupus nephritis class III, IV, +/- V on biopsy within 6 months, UPCR ›1.5, eGFR ›45 mL/min/1.73m2 | 265 | Complete renal response (UPCR ‹0.5, eGFR ›60 mL/min/1.73m2 or ‹20% reduced from baseline | PBO 19.3%, voclosporin low dose 32.6% (odds ratio 2.03 (1.01-4.05); P=0.046), high dose 27.3% (odds ratio 1.59 (0.78-3.27); P=0.2024. | 152 |
| | Active lupus nephritis class III, IV, +/- V on biopsy within 24 months, UPCR ›1.5, eGFR ›45 mL/min/1.73m2 | 357 | Complete renal response (UPCR ‹0.5, eGFR ›60 mL/min/1.73m2 or ‹20% reduced from baseline | PBO 23%, voclosporin 41.4%, OR 2·65; (1.64-4.27), P‹0.0001 | 153 |
| Anifrolumab (IFNAR) | Active lupus nephritis class III, IV +/- V on biopsy within 3 months, UPCR ›1.0, and eGFR ›35 mL/min/1.73m2 | 147 | Difference in mean change from baseline to week 52 in 24 hour UPCR | PBO 70%, anifrolumab 69%, geometric mean ratio 1.03 (0.62-1.71), P=0.905 | 154 |
| Obinutuzumab (CD20) | Active lupus nephritis class III or IV on biopsy within 6 months, UPCR ›1.0, and eGFR ›30 mL/min/1.73m2 | 125 | Complete renal response (UPCR ‹0.5, normal renal function, inactive sediment) | PBO 23%, Obinutuzumab 35%, difference 12% (−3.4% to 28%), P=0.11 | 155 |

BAFF=anti-B cell activating factor; BICLA=BILAG-based composite lupus assessment; BILAG=British Isles lupus assessment group; CI=confidence interval; CLASI=cutaneous lupus area and severity index; DHEA=dehydroepiandrosterone; eGFR=estimated glomerular filtration rate; PBO=placebo, PGA=physician global assessment; PtGA=patient global assessment; SLAM=systemic lupus activity measure; SLEDAI=systemic lupus erythematosus disease activity index; SRI= systemic lupus erythematosus responder index; TYK2=tyrosine kinase 2; UPCR=urine protein creatinine ratio.

*Results for primary outcome measure are shown as reported in the cited publication. Differences, odds ratios, and 95% confidence intervals are shown if reported.

†Variations in SLEDAI versions used exist between studies; all are simply termed SLEDAI in this table.

‡Driven by a ›4 point reduction in SLEDAI.

§Studied in patients with active cutaneous lupus, with or without a diagnosis of systemic lupus erythematosus.

The role of immune complexes in human systemic lupus erythematosus is less clear. Immune complexes are present in kidney biopsies from patients with nephritis,[83] but both affected and unaffected skin in systemic lupus erythematosus are characterized by immune complex deposition[84 85]; the basis of the classical "lupus band test". The question of why and how immune complexes can be constantly present in skin without causing inflammation has not been answered but indicates that other cofactors must be required to drive clinical inflammation. This conclusion raises the question about how critical immune complex deposition is in the pathogenesis of nephritis, despite the subendothelial location of immune complex deposition corresponding to the severity of nephritis.[86] While the exact role of autoantibodies in pathogenesis remains to be elucidated, developments in treatment (see below) support humoral autoimmunity as an ongoing driver of disease in lupus, even though additional functions of B cells outside antibody production include antigen presentation, cytokine production, and cell-cell interactions.

### Innate immunity

Another important early event in the pathogenesis of systemic lupus erythematosus is activation of the innate immune system. This activation is believed to occur in response to stimulation by cellular or nuclear debris, or both, with several possible sources (**fig 1**). The activation is associated with modification and exposure of normally intracellular antigens, which could lead to a loss of immune self-tolerance depending on the individual's genetic and epigenetic background. Supporting this idea, functional impairment of DNASE1L3, an extracellular enzyme capable of digesting chromatin released by apoptotic cells, can lead to a clinical phenotype of systemic lupus erythematosus in humans and mice.[87-89] An alternative mechanism of externalization of intracellular products is the release of neutrophil extracellular traps (NETs). NETosis describes the release of net-like structures containing chromatin and antimicrobial peptides after cell death or non-lytic extrusion.[90] Low density granulocytes represent a distinct subset of neutrophils in systemic lupus erythematosus, with enhanced ability to release NETs, stimulate inflammatory responses, and generate tissue damage, including vascular injury and accelerated atherosclerosis.[91-93] Dysregulation in the complement system also contributes to systemic lupus erythematosus pathogenesis via this pathway, as early components of the classical complement pathway facilitate the removal of apoptotic and damaged cells.[94 95] Exposure of systemic lupus erythematosus neutrophils to immune complexes also induces NETosis, which can further contribute to self-chromatin exposure.[96] Similarly, dysfunctional macrophages can also contribute to impaired phagocytosis of apoptotic bodies in systemic lupus erythematosus.[97]

Exposed intracellular autoantigens, either by themselves or bound to autoantibodies in the form of immune complexes, are engulfed, processed, and presented to T cells by dendritic cells, macrophages, and other antigen presenting cells, leading to the adaptive immune responses to intracellular self-antigens. In addition, nucleic acids are potent inducers of inflammatory responses in their own right. Cells recognize nucleic acids by two main mechanisms: the endosomal toll-like receptors (TLRs) and the cytosolic DNA and RNA sensors. Accumulating evidence in humans and mice suggests essential roles for TLR7 and TLR9 in systemic lupus erythematosus pathogenesis.[98-102] Similarly, recent studies have emphasized the importance of the cytosolic nucleic acid recognition system in systemic lupus erythematosus, particularly the cyclic GMP-AMP synthase/stimulator of interferon genes (cGAS/STING) pathway.[103-105] The TLRs and cytosolic nucleic acid sensing pathways converge into the stimulation of type I interferon production; a protective response when the source of nucleic acids is viral, but almost certainly a key step in systemic lupus erythematosus pathogenesis when the source is the host.

Evidence of exaggerated type I interferon responses is a common finding in systemic lupus erythematosus, and as noted below, blockade of type I interferon signaling has been shown to be a successful therapeutic approach in systemic lupus erythematosus.[106] About half of patients with systemic lupus erythematosus have elevated circulating type I interferon levels, and over two-thirds exhibit an interferon gene expression signature in peripheral blood that is rarely found in healthy individuals.[75 107] Elevated circulating levels of type I interferon are also identified in unaffected relatives of patients with systemic lupus erythematosus, supporting the role of genetics in susceptibility to autoimmunity.[108] The detection of interferon alfa in peripheral blood was shown to be a risk factor for flare in a prospective study of 254 patients in remission,[109] while accordingly, high interferon gene signatures were associated with a higher average disease activity and lower likelihood of reaching treatment goals in a longitudinal study of 205 patients with systemic lupus erythematosus.[76] A recent study using data from a 1756 patient gene expression array dataset with in vitro experimental confirmation observed that while glucocorticoids hardly affect interferon signatures, interferon markedly suppressed glucocorticoid induced genes.[110] These data suggest that interferon contributes to reduced glucocorticoid sensitivity in systemic lupus erythematosus. This conclusion is supported by the enhanced ability to taper glucocorticoids of patients treated with the interferon receptor antibody anifroluma.[111-113][is this OK or is it anifrolumab?]

The source of excess type I interferon activity in systemic lupus erythematosus is not yet certain. Plasmacytoid dendritic cells are distinguished by their ability to produce large amounts of interferon alfa on endosomal TLR stimulation. However, whether

plasmacytoid dendritic cells are a major source of type I interferon in patients with systemic lupus erythematosus remains unresolved.[114] In fact, recent evidence has suggested that circulating plasmacytoid dendritic cells from patients with systemic lupus erythematosus are dysfunctional, and display a senescent phenotype.[115] Beyond type I interferon production, plasmacytoid dendritic cells could play additional roles in systemic lupus erythematosus pathogenesis, as these cells produce other proinflammatory cytokines including interleukin 6, interferon lambda, and chemokines, and can function as antigen presenting cells.[116] However, as noted in **table 2**, the monoclonal antibody litifilimab, which targets the plasmacytoid dendritic cell surface marker BDCA2, has shown promise in phase 2 clinical trials in systemic lupus erythematosus,[144 145] and reduces interferon signatures in systemic lupus erythematosus patient blood and skin.[156]

Alongside plasmacytoid dendritic cells, other cell types have emerged as potential sources of type I interferons in systemic lupus erythematosus, including monocytes/macrophages, follicular dendritic cells, and keratinocytes.[157-160] Caielli et al recently showed the removal of dysfunctional mitochondria in mature red blood cells from patients with systemic lupus erythematosus. These mitochondria carrying red blood cells can stimulate type I interferon production through the cGAS/STING cytoplasmic DNA sensor pathway after undergoing antibody mediated phagocytosis by macrophages.[160] The skin is also likely to contribute to type I interferon production, mainly via the expression of interferon kappa by keratinocytes.[115 158] Interestingly, ultraviolet light exposure to the skin can also drive local and systemic type I interferon responses via cGAS/STING activation.[103]

Overall, growing evidence over the past decade confirmed by clinical trials of interferon-targeting treatments suggests that dysregulation of the innate immune system is crucial in the initiation and perpetuation of systemic lupus erythematosus, with potentially multiple distinct paths to innate immune system dysregulation converging on the clinical systemic lupus erythematosus phenotypes. It remains to be seen whether different origins of innate immune overactivation relate to different clinical phenotypes within the overall systemic lupus erythematosus diagnostic category and, as such, require different treatment approaches.

### Clinical phenotypes of systemic lupus erythematosus

Setting aside the challenge of problematic classification of a heterogeneous set of phenotypes under a single diagnostic rubric, patients classified with systemic lupus erythematosus have highly heterogeneous clinical manifestations. Constitutional symptoms such as fever, brain fog, and especially fatigue affect most patients; fatigue is rated by patients among the highest impact features of their disease and is a major driver of low quality of life reported by patients with systemic lupus erythematosus.[161 162] Inflammatory arthropathy and mucocutaneous disease are seen in most patients, while glomerulonephritis and hematological disease, each seen in about 50% of patients, are the most

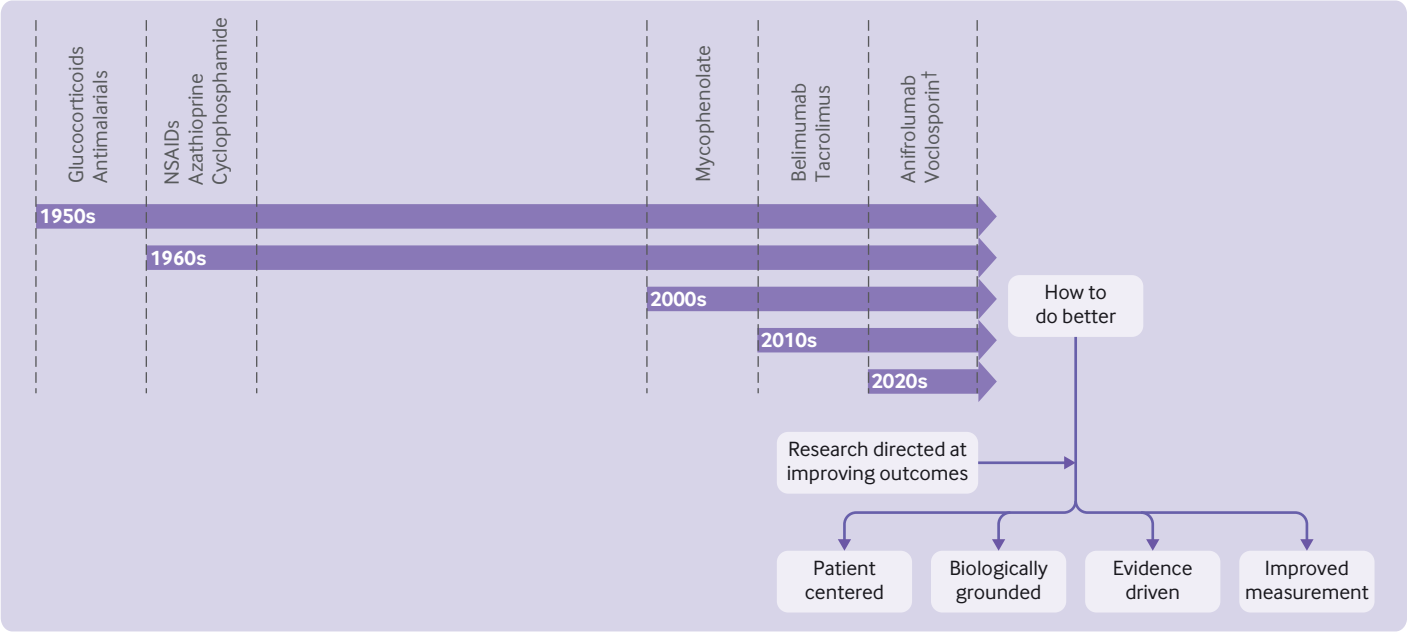


**Fig 2 | Timeline of treatments for systemic lupus erythematosus, and a roadmap for future progress. Many drugs forming the standard of care for systemic lupus erythematosus have been in use since the 1950s, with no new treatments being approved for decades until the approval of belimumab in 2011. Improving on this history requires that research be specifically focused on doing so, including a patient centered and biologically grounded approach to the study of systemic lupus erythematosus, evidence based decision making in clinical practice, as well as improved measurements to increase the utility of clinical trial data, even negative data. NSAID=non-steroidal anti-inflammatory drug. †Approved for lupus nephritis**

common other organ domains affected.[163] Further heterogeneity exists within each organ system; for example, multiple types of skin, joint, and renal disease are recognized. Neuropsychiatric lupus is less common, but also represents a broad catalogue of manifestations.[164] As recently reviewed,[165] cognitive dysfunction is commonly reported by patients with systemic lupus erythematosus, but a recent cross sectional study suggested a poor correlation between patient reported cognitive symptoms and objective findings.[161] Consistent with the multisystem nature of systemic lupus erythematosus, the list of other manifestations of systemic lupus erythematosus is long, and includes serositis, gastrointestinal disease, ocular disease, hepatitis, heart disease, and lung disease. Importantly, systemic lupus erythematosus is also heterogeneous in its time course, with some patients manifesting features all at once and others in an unpredictable series of steps over months or years. Similarly, the time course of disease activity varies greatly between patients, from relapse and remission in some to persistently active disease in others.[166] Of note, when systemic lupus erythematosus begins in childhood, it often takes a more severe form, characterized by higher rates of lupus nephritis, anti-dsDNA antibody positivity, and hemolytic anemia, as well as higher disease activity, morbidity, and mortality than adult onset systemic lupus erythematosus.[167]

Antiphospholipid syndrome, in which autoantibodies to antigens with roles in the coagulation system (such as β2 glycoprotein 1) are associated with clinical manifestations including arterial and venous thrombosis, pregnancy loss, and thrombocytopenia, can occur in patients with systemic lupus erythematosus as well as de novo (primary antiphospholipid syndrome). Please see the recent *BMJ* State of the Art review on this topic for more information.[168]

## Treatment of systemic lupus erythematosus

### Goals of treatment

As noted below in the guidelines section, a paucity of robust evidence and the clinical heterogeneity of the disease hamper the ability to provide clear guidance to practitioners on how to treat systemic lupus erythematosus; lupus nephritis is an exception in that several studies have compared treatment approaches for this manifestation.

The overarching goals of treatment for systemic lupus erythematosus are to reduce disease activity, prevent irreversible organ damage, and retain quality of life. These goals are achieved through seeking remission, or if remission cannot be attained, a state of low disease activity. As glucocorticoids contribute to the risk of long term harm in systemic lupus erythematosus, remission and low disease activity concepts in systemic lupus erythematosus combine the requirement for low disease activity with a requirement for low glucocorticoid doses. These goals are, unfortunately, not reflected in primary outcome measures used in systemic lupus erythematosus clinical trials. As a result, translation of clinical trials into clinical practice is not directly guided by trial results and requires considerable interpretation by clinicians. Fortunately, the low disease activity and remission definitions have now been shown to be achievable and highly discriminatory in post hoc analysis of clinical trial datasets,[169-171] and, as a result, now appear as key secondary outcome measures in more recent trials[142 143 147]; this should allow for a more direct application of trial outcomes to the goals of care in future.

Due to the lack of evidence directly linking treatments to treatment goals, the information that follows is organized by drug class, with the general guidance that the least harmful treatment that maintains control of disease activity should be used.

### Antimalarials

A core tenet of drug treatment for systemic lupus erythematosus is that treatment with an antimalarial (usually hydroxychloroquine) is recommended for all patients unless contraindicated. Although prospective studies are lacking, analysis of a longitudinal inception cohort of 1460 patients followed for 20 years indicated that antimalarials reduce the frequency of flares,[172] and another study of 6241 patients indicated that hydroxychloroquine use was associated with reduced mortality.[173] Confirming these results, a study of whole blood and serum hydroxychloroquine concentrations in 573 patients with systemic lupus erythematosus showed an association between drug level and avoidance of active disease[174]; this and similar studies[175] also revealed high rates of non-adherence to standard treatment in patients with systemic lupus erythematosus that further complicate management. Adverse effects of hydroxychloroquine include rash, gastrointestinal discomfort, and uncommonly, skin pigmentation (incidence of approximately 7%)[176] and retinal toxicity (overall prevalence of 7.5%, with increase to 20% after 20 years of treatment). Retinal toxicity has led to a recommendation of a maximum dose of 5 mg/kg/day (actual body weight) based on a retrospective case-control study in 2361 patients with at least 5 years of exposure.[177] A joint statement of professional rheumatology, dermatology, and ophthalmology societies has highlighted the need for screening for retinal toxicity, but also the safety of long term hydroxychloroquine when appropriate precautions are taken.[178] A minority of patients have adequate control of disease with non-drug measures and antimalarials alone. Treatment guidelines[179 180] suggest the addition of glucocorticoids and immunosuppressants, or both, in this setting, and these drugs are often started when disease is moderately severe or severe at onset.

### Glucocorticoids

Glucocorticoids are a mainstay of both acute and chronic treatment of systemic lupus erythematosus. Large multicenter multinational longitudinal cohort studies show that glucocorticoids are used

in as many as 80% of patients with systemic lupus erythematosus.[181 182] Unfortunately, in addition to predictable dose dependent Cushingoid metabolic adverse effects, glucocorticoids are associated with increased accrual of irreversible organ damage.[183 184] As a result, lowering glucocorticoid exposure is a major goal of systemic lupus erythematosus management. However, a trial in which 124 patients with quiescent disease were randomized to continue or stop oral glucocorticoids found that flares were less frequent in those who did not stop glucocorticoids (risk ratio 0.2, 95% confidence interval 0.1 to 0.7).[185] This result suggests that new treatments are needed to allow patients to stop using steroids.

### Immunosuppressants

Immunosuppressants used in systemic lupus erythematosus, including mycophenolate mofetil and mycophenolate sodium, azathioprine, and less commonly used agents such as methotrexate are almost always used in combination with glucocorticoids and antimalarials. Other than for lupus nephritis, the specific choice of immunosuppressants in different presentations lacks evidence from high quality studies, but increasingly mycophenolate mofetil is seen as the first line immunosuppressant for systemic lupus erythematosus.

A randomized trial comparing mycophenolate mofetil with azathioprine in 240 patients with non-renal systemic lupus erythematosus showed that enteric coated mycophenolic acid was superior in attainment of remission (32.5% *v* 19.2%, treatment difference 13.3, 95% confidence interval 2.3 to 24).[186] A prospective cohort study of over 700 visits in 50 patients with childhood onset systemic lupus erythematosus suggested that early introduction of mycophenolate was associated with increased attainment of treatment goals and lower overall exposure to glucocorticoids, as evidenced by mycophenolate mofetil usage being associated with reaching a lupus low disease activity state (LLDAS) within six months on multivariable analysis, and 53% of children achieving clinical remission on treatment versus only 22% achieving clinical remission off immunosuppressants.[187] The optimal duration of immunosuppressant treatment in systemic lupus erythematosus is poorly evidenced, but a recent multinational cohort study of over 3000 patients suggested that treatment retention as a surrogate for efficacy and tolerability is poor for both azathioprine and mycophenolate mofetil, with cessation of 25% of treatment episodes with mycophenolate mofetil occurring by 175 days; treatment retention, however, is better for mycophenolic acid (387 days to discontinue 25% of treatment episodes).[188]

Treatment guidelines for lupus nephritis are regularly updated by an international glomerulonephritis working group, with the most recent guidelines recommending treatment of histological class III or IV lupus nephritis with mycophenolate mofetil or cyclophosphamide for induction, and mycophenolate mofetil for maintenance; the optimal duration of maintenance treatment is unknown but should not be less than four years. Importantly, guidelines now recommend reduced starting doses of intravenous and subsequent oral glucocorticoids compared with historical practice and tapering to 7.5 mg/day prednisolone (or equivalent) or less within six months for most patients.[189 190]

For severe organ threatening disease in other systems, treatment approaches are frequently derived from guidelines for lupus nephritis.[179]

### Biological treatments and calcineurin inhibitors

The first biological widely used in the treatment of systemic lupus erythematosus is the anti-CD20 B cell depleting chimeric monoclonal antibody, rituximab. After multiple case reports suggesting benefit, randomized trials of rituximab in both systemic lupus erythematosus and lupus nephritis were performed, but both were negative.[120 149] Despite these results, the volume of anecdotal reports and multiple case series showing responses in refractory patients treated with rituximab[191 192] mean that the drug is widely used in patients unresponsive to immunosuppressants; generally, when other treatments have failed.

In recent years, three new treatments have been approved for systemic lupus erythematosus after several decades without new lupus medicines (**fig 2,table 2**). The BAFF monoclonal antibody belimumab had a negative phase 2 trial in systemic lupus erythematosus, but post hoc analysis allowed the investigators to derive a novel outcome measure, the systemic lupus erythematosus responder index (SRI),[193] which was used in the two phase 3 trials that led to regulatory approval. Belimumab was shown to be superior to placebo for attainment of SRI in two randomized trials of 867 and 819 patients[123 124] (**table 2**); a similar efficacy was confirmed in trials of a subcutaneous form,[194 195] and notably, in a randomized trial in 93 children with systemic lupus erythematosus.[196] A recent systematic review of these trials and several postmarketing and registry based studies concluded that belimumab was effective in patients with serologically active disease (ie, in the presence of anti-dsDNA antibodies or low serum complement), reduces organ damage accrual, and is well tolerated.[197] Reduced damage accrual in response to belimumab treatment was suggested in a study comparing data from the phase 3 trials of belimumab with propensity matched data from a large single center cohort.[198] Most recently, a phase 3 trial of belimumab in 448 patients with lupus nephritis showed superiority to placebo over two years,[151] with both arms also receiving induction treatment with either mycophenolate mofetil or cyclophosphamide, leading to its approval for this indication by the US Food and Drug Administration in 2020. These studies confirm the pathogenic role of BAFF, and hence of B cells, in systemic lupus erythematosus. Of note, belimumab is considered

safe in lupus nephritis patients with reduced renal function, which is not yet confirmed for calcineurin inhibitors such as voclosporin (see below).

In parallel, the importance of the innate immune system in systemic lupus erythematosus has been confirmed by trials of anifrolumab, an antibody to the type I interferon receptor. After a positive phase 2 randomized trial in 305 patients,[199] two phase 3 trials were completed. The first, in 457 patients, was a negative study based on the primary outcome measure of SRI, although numerous secondary outcome measures were nominally positive[113] (**table 2**). The second, using a different endpoint, was positive for the primary and many secondary outcomes,[112] and anifrolumab was approved in 2021-22 in multiple jurisdictions. Subsequent post hoc analyses suggest efficacy across multiple organ domains, reduction in flares, and glucocorticoid sparing effects of anifrolumab.[111 200 201] Safety considerations for anifrolumab include increased herpes zoster reactivation and upper respiratory infections.[202] Importantly, a long term extension study in which 547 patients from the phase 3 trials were re-randomized to placebo or anifrolumab 300 mg monthly if they had been on placebo, or continued on anifrolumab 300 mg monthly if they had been on anifrolumab, showed no new safety signals compared with the first year of treatment, as well as long term trends towards both reduced disease activity and reduced glucocorticoid dosing in anifrolumab treated patients.[203] A phase 2 trial of anifrolumab in 147 patients with lupus nephritis was negative,[154] but suggestions of efficacy in secondary outcome measures have prompted a phase 3 trial to be initiated in this indication.

Finally, the novel calcineurin inhibitor voclosporin was shown to be effective compared with placebo in a phase 3 study of 357 patients with lupus nephritis[153] in which all patients also received mycophenolate mofetil, and this drug received regulatory approval in 2021. The actions of voclosporin include effects on T lymphocytes and podocytes. These results come after several encouraging studies of an older calcineurin inhibitor, tacrolimus; for example, a study of 150 patients showing non-inferiority compared with mycophenolate mofetil.[204]

### Outcomes with current treatment

Despite recent approvals of new treatments, outcomes for patients with systemic lupus erythematosus remain poor. A longitudinal cohort study of over 3300 patients identified that up to one-third do not achieve treatment goals, and that failure to do so is associated with worse outcomes in terms of irreversible organ damage, health related quality of life, and mortality.[205] This finding is supported by smaller studies showing that failure to achieve low disease activity soon after diagnosis is associated with increased mortality and organ damage.[206 207] In an international meta-analysis representing data from Asia, Europe, and North America from 1999 to2020, the overall standardized mortality ratio for patients with systemic lupus erythematosus was 2.6.[208] After some improvements in survival were observed in the second half of the 20th century,[209] a study of over 11 million people in a UK NHS dataset[210] showed no improvement in survival of patients with systemic lupus erythematosus this century. The leading causes of death in patients with systemic lupus erythematosus include infection related to immunosuppression, renal disease, and cardiovascular disease.[209] In a prospective cohort study of 3811 patients, socioeconomic factors and smoking were identified as risk factors for mortality, alongside disease activity and glucocorticoid exposure.[211] Poor health related quality of life, rated among the highest concerns of patients with systemic lupus erythematosus,[162] has been shown in many studies, as summarized in a recent review.[212]

The evidence of poor outcomes for patients with systemic lupus erythematosus underlines the need for improved treatments, and treatment strategies, for this disease. Emerging medicines are based on a deepening understanding of the biology of systemic lupus erythematosus.

### Treat-to-target approaches

While new medicines will be needed, improvements in outcome in systemic lupus erythematosus can also be achieved through better use of current treatments. Stemming from two papers in 2014 outlining consensus on the need for treat-to-target strategies in systemic lupus erythematosus and a pathway to develop them,[213 214] treat-to-target approaches are now reflected in treatment guidelines for systemic lupus erythematosus. These approaches require not only low or absent disease activity but also, given the evidence of long term harm from their use, ceilings in glucocorticoid dose. The definition of remission in systemic lupus erythematosus (DORIS) group reported a consensus definition of remission which rests on the absence of clinical disease activity and a prednisolone (or equivalent) ceiling of 5 mg/day.[215] As remission is infrequently achieved in systemic lupus erythematosus, LLDAS (embodying the absence of severe disease activity or flare), and a low treatment burden with a prednisolone ceiling of 7.5 mg/day, have also been defined.[216] These goals of treatment have been validated in cohort studies and prospective studies as protective from organ damage accrual, mortality, and loss of quality of life,[205 211 217 218] including in a 1735 patient multicenter prospective study.[219 220] In the prospective cohort study of 3811 patients mentioned above, attainment of LLDAS or remission was protective from mortality, and steroid free remission was markedly more protective.[211] Attainment of remission or LLDAS has been shown to be associated with improved health related quality of life in a 1422 patient cross sectional study,[218] and in post hoc analysis of clinical trials of belimumab and anifrolumab.[171 221]

Formal prospective strategy trials are needed to show whether treat-to-target approaches (eg, adjusting treatment in a metric based way based

on these targets) improves outcomes; a protocol for such an intervention study has been published.[222] Importantly for using new treatments to achieve these goals, rates of LLDAS attainment were improved by the addition of biological treatment to standard of care; this finding comes from a post hoc analysis of responses to belimumab using data from 1684 patients enrolled in phase 3 trials,[221] and responses to anifrolumab using data from 305 and 819 patients from the phase 2 and pooled phase 3 trials, respectively.[169 171] LLDAS attainment was included a priori as an outcome measure in phase 2 trials of baricitinib and the tyrosine kinase 2 (TYK2) inhibitor deucravicitinib, and in both cases, superior rates of LLDAS attainment were observed with active treatment compared with placebo.[147 223]

### New combinations of existing treatments

In the absence of multiple new treatments with which to apply to a treat-to-target approach, other strategies rely on new combinations of existing treatments. For example, in a randomized open label trial in refractory lupus nephritis, the combination of rituximab with cyclophosphamide was followed by either placebo or monthly belimumab.[224] This study of 46 patients did not show any efficacy advantage for the addition of belimumab after induction treatment, but the lack of concerning safety signals was reassuring for future studies of combination or sequential treatments. Another study, whose design has been published[225] but results only reported in conference abstract form,[226] randomized 292 patients with active systemic lupus erythematosus to belimumab with or without the addition of two doses of rituximab or placebo, or belimumab plus standard of care. The addition of rituximab showed no advantage; as all patients received belimumab no further conclusions could be drawn. Finally, a small trial of 52 patients treated with rituximab were randomized to either placebo or belimumab for 52 weeks thereafter.[227] In this study, the primary outcome measure of lower anti-dsDNA antibody titer was met, and belimumab treatment was associated with a significantly lower rate of flares.

Similar results have been shown with the use of belimumab alone; therefore, whether the sequential combination offers advantages is unclear. Reassuringly, no concerning safety signals were observed.

## Emerging treatments

The evolution of novel treatment development in systemic lupus erythematosus broadly parallels two sets of advances: increasing understanding of its pathogenesis and slowly improving execution of clinical trials. In **table 2**, we summarize in chronological order the results of clinical trials of novel agents in systemic lupus erythematosus and lupus nephritis. The timeline suggests that while phase 2 trial success rates are improving over time, difficulties remain in translating positive phase 2 results into phase 3 and product registration. Despite positive phase 2 results, phase 3 trials of the JAK inhibitor baricitinib returned mixed results, with one showing superior attainment of SRI compared with placebo,[142] but the other parallel and effectively identical trial showing no difference.[143] Trials of the anti-BAFF antibody tabalumab, which had negative results in two phase 3 trials enrolling a total of 2288 patients,[128 228] resulted in its development being terminated, and a similar fate befell the interleukin 12/23 inhibitor ustekinumab, for which phase 3 trials were negative despite positive phase 2 studies.[140 141] Factors leading to negative trial results include high placebo response rates, and conflicting findings between studies on the same product; these factors drove a multinational panel to conclude recently that improved study design and endpoints are among the highest priorities in systemic lupus erythematosus.[229 230]

Encouraging results in earlier stage trials continue to emerge. A potent CD20 targeting mAb, obinutuzumab, had a positive result in a phase 2 randomized trial in 125 patients with lupus nephritis,[155] and case series suggest it could be effective in patients with systemic lupus erythematosus who have failed rituximab[231]; phase 3 trials of this agent in both systemic lupus erythematosus and in lupus nephritis are under way (NCT04963296, NCT05039619). This set of results suggests that deeper B cell depletion could be more effective in systemic lupus erythematosus, a concept further supported by remarkable reports of complete remission in highly treatment refractory patients with systemic lupus erythematosus treated with CD19 directed chimeric antigen receptor T cell (CAR-T) treatment[232 233]; however, CAR-T treatment and other B cell depleting strategies have not been directly compared. A phase 2 trial randomized patients to placebo or the oral TYK2 inhibitor deucravacitinib[147] and found that the primary outcome measure of SRI and all secondary outcome measures, including attainment of LLDAS, were met.

## Guidelines

Several national and international societies have published guidelines for treating systemic lupus erythematosus, including the American College of Rheumatology, and more recently, EULAR.[179 180] These guidelines are chiefly based on expert consensus, as prospective studies comparing treatment strategies for systemic lupus erythematosus are lacking. They emphasize important non-drug strategies, including avoidance of ultraviolet radiation, management of cardiovascular risk factors, vaccinations, and thromboprophylaxis where indicated.

The most recent guidelines,[179] published in 2019 by a EULAR consensus group, define the overarching goal of systemic lupus erythematosus care as aiming to minimize disease activity across all organ systems while maintaining the lowest possible burden of treatment toxicity. In these guidelines, which predate the approval of anifrolumab and voclosporin, antimalarial use is

recommended for all patients with systemic lupus erythematosus unless contraindicated. Additional treatments are guided by broad categories of severity of active disease. Mild disease, characterized as constitutional symptoms, mild rash or arthritis, and thrombocytopenia with a platelet count no less than 50 000/mm$^3$, is recommended to be treated with the addition of glucocorticoids. Moderate disease activity, characterized as rheumatoid-like arthritis, more severe skin disease or cutaneous vasculitis affecting <18% of body surface area, serositis, or thrombocytopenia with a platelet count no less than 20 000/mm$^3$, is recommended to be treated with the addition of immunosuppressives to antimalarials and glucocorticoids (options include methotrexate, azathioprine, mycophenolate, or calcineurin inhibitors, with the addition of belimumab in refractory cases). Severe disease activity, categorized as major organ threatening disease such as kidney and central nervous system disease, is recommended to be treated with the addition of mycophenolate, cyclophosphamide, or rituximab. These categories of severity are also listed according to the systemic lupus erythematosus disease activity index (SLEDAI) and British Isles lupus assessment group (BILAG) disease activity measures, but these are rarely used outside the research setting; the guidelines also highlight that most of these recommendations are not derived from level A evidence. Glucocorticoids are recommended across the entire spectrum of disease, which reflects a paucity of safe effective alternatives for the treatment of systemic lupus erythematosus. Similar guidelines were also published in 2019 for childhood onset systemic lupus erythematosus,[234] albeit with an even shallower evidence base.

## Conclusion

We look forward to a future where optimism can replace the guarded prognostic discussions that still characterize our conversations with patients with systemic lupus erythematosus today. Notwithstanding ongoing concerns with trial and endpoint design, the information in **table 2** highlights a remarkable increase in clinical development activity in systemic lupus erythematosus over the past two decades but, unfortunately, successes leading to new product approvals are uncommon. To improve our ability to deliver better outcomes for patients, research efforts should shift towards a focus on just that: improving the lives of patients. This shift requires patient centered approaches, application of advances in pathogenic understanding to identification and testing of therapeutic targets, evidence based decision making in clinical practice, and improved robustness of outcome measures used in trials to improve the utility of both positive and negative results (**fig 2**). Reclassification of systemic lupus erythematosus into subsets based on biological profiles could help in the assignment of individual patients to the treatments best suited to them, which potentially include combinations of adaptive and innate immune targeting medicines; importantly, this approach could also result in reclassification of autoimmune diseases as a class into a system based on molecular profiles rather than clinical clusters.[11] Alternatively, single organ studies with specific readouts could result in a variety of basket trial approaches, some of which are now being cautiously introduced (NCT05162586). Antigen specific approaches have had proof of concept in other autoimmune diseases[235] and could lead to a patient-by-patient approach; alternatively, the discovery that GILZ mediates the effects of glucocorticoids in systemic lupus erythematosus but lacks metabolic toxicity[51 53] could lead to a broad spectrum approach obviating the need for detailed immune profiling. Regardless, as outcomes including death in systemic lupus erythematosus are closely linked to socioeconomic factors, future advances in treatment must be made available to patients around the world.

### QUESTIONS FOR FUTURE RESEARCH

- Should systemic lupus erythematosus and related autoimmune diseases be reclassified using biological, rather than clinical, descriptors?
- Should we continue to study treatments in pooled patients with systemic lupus erythematosus, or in organ specific patient groups or biologically determined subsets?
- How should we measure treatment response in systemic lupus erythematosus trials in the future?
- Will the combination of innate plus adaptive immune targeting be necessary to completely control disease activity in systemic lupus erythematosus, or does the link between them mean that targeting one is sufficient?

### GLOSSARY OF ABBREVIATIONS

- SLICC: systemic lupus international collaborating clinics
- EULAR: European Alliance of Associations for Rheumatology
- PTPN22: protein tyrosine phosphatase non-receptor type 22
- GILZ: glucocorticoid induced leucine zipper
- BAFF: anti-B cell activating factor
- NETs: neutrophil extracellular traps
- TLRs: toll-like receptors
- cGAS/STING: GMP-AMP synthase/stimulator of interferon genes
- LLDAS: lupus low disease activity state
- SRI: systemic lupus erythematosus responder index
- DORIS: definition of remission in systemic lupus erythematosus group
- TYK2: tyrosine kinase 2
- CAR-T: chimeric antigen receptor T cell
- SLEDAI: systemic lupus erythematosus disease activity index
- BILAG: British Isles lupus assessment group

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