Novel paradigms in systemic lupus erythematosus

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The heterogeneity of systemic lupus erythematosus (SLE), long recognised by clinicians, is now challenging the entire lupus community, from geneticists to clinical investigators. Although the outlook for patients with SLE has greatly improved, many unmet needs remain, chief of which is the development of safer and more efficacious therapies. To develop innovative therapies, a far better understanding of SLE pathogenesis as it relates to the array of clinical phenotypes is needed. Additionally, to efficiently achieve these goals, the lupus community needs to refine existing clinical research tools and better adapt them to overcome the obstacles created by the heterogeneity of manifestations. Here, we review progress towards the ultimate goal of safely reducing disease activity and preventing damage accrual and death. We discuss the new classification criteria from the European League Against Rheumatism and American College of Rheumatology, novel definitions of remission and low lupus disease activity, and new proposals for the histological classification of lupus nephritis. Recommendations for the treatment of SLE and novel approaches to drug development hold much promise to further enhance SLE outcomes.

Introduction

Systemic lupus erythematosus (SLE) is not only the prototypic systemic autoimmune disease, but also one of the most heterogeneous illnesses treated by physicians (panel 1). This heterogeneity presents immense challenges to diagnosis, treatment, and therapeutic advances. Despite these hurdles, SLE mortality has declined from 50% in the pre-corticosteroid era (circa 1948) to a 15-year survival of 85–95% in the modern era.[1,2] Although new therapies are largely responsible for improved outcomes, earlier diagnosis and better management of specific organ manifestations and complications, particularly those related to lupus nephritis, have also benefited patients. However, excessive damage accrual, morbidity, and mortality remain,[3] indicating that a substantial medical need in SLE still exists. This Review highlights recent advances in the field and presents current treatment algorithms, the new European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification of SLE, new outcome measures, a proposal to modify the histological classification of lupus nephritis, and novel drug development strategies.

Search strategy and selection criteria

We searched for full-text English language articles in the PubMed database with the search terms "systemic lupus", "lupus nephritis", "DMARDs", "biologics", "remission", "treat to target", "antimalarials", "calcineurin inhibitors", "MMF/mycophenolate", "rituximab", "Jak inhibition", "atacicept", "belimumab", "ustekinumab", and "new therapies", alone and in specific combinations. The date of our last search was Jan 31, 2019. We evaluated the retrieved papers and selected the most appropriate articles. We also searched for recommendation papers by international and national societies, as well as abstracts presented at the European League Against Rheumatism or American College of Rheumatology congresses in 2017 and 2018, with the search terms noted above.

Panel 1: Heterogeneity in systemic lupus erythematosus

Pathogenesis

- Non-exclusive genetic association with *HLA-DR3* and *HLA-DR15* heterozygosity and other risk alleles (eg, *PTPN22*)
- Various abnormalities in the phenotypes and function of myeloid (dendritic cells, plasmacytoid dendritic cells) and lymphoid (T cells, plasma and B-cell subsets) cells
- Individual imbalances in proinflammatory versus anti-inflammatory cytokines and chemokines
- Heterogeneity of the frequency and functionality of regulatory T cells and regulatory B cells
- Heterogeneity of autoantibodies

Clinical manifestations, disease course, and prognosis

- Individual organ and tissue manifestations—ie, presence of skin, joint, or haematological manifestations, or lupus nephritis
- Individual course of the disease (relapsing remitting, persistently active, clinically quiescent serologically active, prolonged remission)
- Various complications, damage accrual, and type of end-stage organ failure

Laboratory findings

- Variations in anti-nuclear antibodies (titre and pattern)
- Presence or absence of anti-double-stranded DNA antibodies
- Presence or absence of anti-extractable nuclear antigen antibodies (Sm, Ro, La, RNP)
- Presence or absence of C3 or C4 hypocomplementaemia
- Presence or absence of type 1 interferon signature, or B-cell or plasma cell signatures

Treatment response and tolerability

- Distinct treatment responses to conventional disease-modifying antirheumatic drugs (eg, azathioprine, methotrexate, mycophenolate mofetil) for different organ domains
- Variation in safety and tolerability of disease-modifying antirheumatic drugs and biological therapies

Epidemiology and diagnosis

Epidemiology

The prevalence of SLE has been estimated to be 30–50 per 100 000, which equates to approximately 500 000 patients in Europe and 250 000 in the USA.[4,5] An analysis published in 2017 provided evidence that ancestry, race, and ethnicity have major impacts on SLE manifestations and severity.[6] The incidence and prevalence of SLE are higher in black, Asian, and Hispanic patients, who tend to develop lupus earlier and have more severe and more active disease, with long-term disease damage and increased mortality, than do white patients.[6,7] Observed disparities are largely related to genetic differences and exposures to local environments. 90% of patients are women, and they are generally of childbearing age. Although presenting manifestations are rather diverse, common ones include constitutional symptoms, rash, and arthritis. At the other end of the spectrum, patients can present with severe organ-threatening complications, such as lupus nephritis, autoimmune cytopenias, or nervous system disease.

EULAR and ACR revised classification of SLE

A joint multinational effort by the ACR and EULAR, due to be published in 2019, has led to the development of new classification criteria for SLE.[8] This initiative aimed to exclude lupus mimickers and focus on true autoimmune disease, and promote applicability to juvenile and early SLE. The derivation process arrived at a threshold, above which experts would classify patients as having SLE for the purpose of clinical study inclusion. Ten hierarchical domains (seven clinical and three immunological), consisting of a total of 22 criteria with distinct weights, were identified with the requirement of a total score of 10 or higher for an individual patient to meet the criteria for SLE classification[8] (figure 1). Validation provided a sensitivity of 96·1% compared with the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (validation cohort: 96·7%)[10] and the 1997 ACR criteria (validation cohort: 82·8%).[11] The EULAR and ACR criteria yielded a specificity of 93·4% (SLICC validation cohort: 83·7%; 1997 ACR validation cohort: 93·4%).

Not surprisingly, anti-nuclear antibodies are the key biomarker and entry criterion for the EULAR–ACR SLE classification. In a phase 1 early SLE cohort, 99·5% of the 389 patients with SLE tested positive for anti-nuclear antibodies.[9] A systematic literature review and meta-regression of data on 13 080 participants showed that an anti-nuclear antibody titre of 1:80 or greater has a sensitivity of 98%, with a lower limit of the 95% CI of 97·0%.[9] The frequencies of anti-nuclear antibody-positive patients with SLE in the derivation (99·6%) and validation (99·3%) cohorts used in the EULAR–ACR SLE classification were similar.[8] Anti-nuclear antibodies can also occur in patients with isolated autoimmune conditions (eg, thyroiditis, autoimmune hepatitis) and in those taking specific drugs (eg, anticonvulsants, tumour necrosis factor inhibitors, antidepressants), and are not an exclusive signature of SLE. Although some patients with SLE are anti-nuclear antibody negative, the new EULAR–ACR criteria do not allow for their classification.[9,12] Additional laboratory variables were nominated, such as increased circulating BAFF (also known as TNFSF13B), IP10 (CXCL10), MCP (CCL2), or TNF, the type 1 interferon signature, or increased T-helper cell 17 and plasma cell signatures, but low assay availability in the clinical setting and insufficient evidence led to their exclusion.[13]

Anti-nuclear antibody faces a renaissance given its stature in the EULAR–ACR classification scheme.[14] International[15] and ACR[16] recommendations for anti-nuclear antibody diagnostics consider human epithelial cell immunofluorescence as the gold standard. Its

Entry criterion
Anti-nuclear antibodies at a titre of ≥1:80* on HEp-2 cells or an equivalent positive test

Additive criteria
Do not count a criterion if an explanation other than systemic lupus erythematosus is more likely
Occurrence of a criterion on at least one occasion is sufficient
At least one clinical criterion is required
Criteria need not occur simultaneously
Within each domain, only the highest weighted criterion is counted toward the total score

Clinical domains and criteria	Weight	Immunological domains and criteria	Weight
Constitutional		**Anti-phospholipid antibodies**	
Fever	2	Anti-cardiolipin antibodies or anti-β2GP1 antibodies or lupus anticoagulant	2
Cutaneous		**Complement proteins**	
Non-scarring alopecia	2	Low C3 or low C4	3
Oral ulcers	2	Low C3 and low C4	4
Subacute cutaneous or discoid lupus	4		
Acute cutaneous lupus	6		
Arthritis		**Highly specific antibodies**	
Either synovitis characterised by swelling or effusion in ≥two joints or tenderness in ≥two joints plus ≥30 min of morning stiffness	6	Anti-dsDNA antibody†	6
		Anti-Smith antibody	6
Neurological			
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Haematological			
Leucopenia	3		
Thrombocytopenia	4		
Autoimmune haemolysis	4		
Renal			
Proteinuria >0·5 g/24 h	4		
Renal biopsy class II or V lupus nephritis	8		
Renal biopsy class III or IV lupus nephritis	10		

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled

Figure 1: **2019 European League Against Rheumatism and American College of Rheumatology classification criteria for systemic lupus erythematosus**
dsDNA=double-stranded DNA. HEp-2=human epithelial type 2. *Anti-nuclear antibody positivity should take the individual cutoff into account; the titre 1:80 has been derived from a broad literature review.[9] †In an assay with ≥90% specificity against relevant disease controls.

Panel 2: Lupus low disease activity state

The following criteria for a low disease activity state in patients with systemic lupus erythematosus were proposed by Franklyn and colleagues.[22]

Disease activity

- SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity
- No new features of lupus disease activity compared with the previous assessment
- SELENA-SLEDAI PGA score of ≤1 (scale 0–3)

Immunosuppressive medications

- Current prednisolone (or equivalent) dose ≤7·5 mg daily
- Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs

SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000. SELENA–SLEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index. PGA=Physician Global Assessment.

Panel 3: Operational definition of remission in systemic lupus erythematosus

The following framework is based on a definition of remission in systemic lupus erythematosus (known by its acronym DORIS) that was proposed by van Vollenhoven and colleagues.[23] They propose that remission in systemic lupus erythematosus is a durable state characterised by the following symptoms, signs, and laboratory tests:

Clinical disease activity

A validated index must be used:

- SLEDAI <2
- Clinical SLEDAI=0
- Clinical ECLAM=0
- BILAG D and E only

PGA score of <0·5

Serological activity

- Absence of anti-DNA antibodies
- Correction of abnormal complement concentration

Treatment

Patients can still be treated with:

- Antimalarials
- Corticosteroids ≤5 mg

Duration of remission

≥6 months to ≥5 years*

BILAG=British Isles Lupus Assessment Group. ECLAM=European Consensus Lupus Activity Measurement. PGA=Physician Global Assessment. SLEDAI=Systemic Lupus Erythematosus Disease Activity Index. *The exact duration of remission is still to be determined.

proper use provides additional qualitative information in the form of anti-nuclear antibody patterns. These patterns are characteristic of the underlying autoantibodies (ie, homogeneous for anti-double-stranded DNA [dsDNA] antibodies and nucleosome; fine speckled for anti-Ro or anti-La antibodies) and have (almost forgotten) diagnostic importance. A major challenge of anti-nuclear antibody testing, even after semi-automatisation, is the absence of standardisation.[17] Among the family of anti-nuclear antibodies, uniquely occurring antibodies against dense fine-speckled 70 kD proteins have been reported to largely exclude connective tissue disease from diagnostic consideration.[18] From a clinical perspective, the utility of anti-nuclear antibodies must be balanced with their shortcomings, but remain key for classifying SLE.

A novel clinical criterion in the EULAR–ACR classification—unexplained fever—is relatively common, especially for early disease. A renal biopsy sample yielding a diagnosis of International Society of Nephrology (ISN) and Renal Pathology Society (RPS) class III or IV lupus nephritis has the greatest weight (10 points) and allows classification by itself. This is consistent with the SLICC classification criteria.[10]

The multiphase methodological approach and ensuing classification system using anti-nuclear antibodies as an entry criterion and weighted, hierarchically clustered criteria, constitute a paradigm shift in the classification of SLE. These criteria have improved face validity because the structure and weighting reflect the perspective of an international community comprising more than 200 multinational SLE experts across several medical disciplines.

Classification versus diagnosis

The aforementioned EULAR–ACR criteria are classification criteria as opposed to diagnostic criteria. Classification criteria define cohorts with high specificity for clinical research studies, whereas diagnosis will remain a more subjective clinician-dependent process that might yield lower specificity.

Although the value of an anti-nuclear antibody test is upheld by it being the gateway to SLE classification, it often is the bane of rheumatologists who are referred patients with non-specific symptoms on account of a positive anti-nuclear antibody test. In the past 2–3 years, assays such as AVISE CTD (Exagen, Vista, CA, USA), which incorporates the presence of cell-bound complement activation products into a multicomponent assay, and SLE-key (ImmunArray, Richmond, VA, USA), a 200-antigen immunochip, have become available to assist clinicians in diagnosing SLE.[19,20] Use of such technologies by clinicians is dependent on the clinician's confidence in diagnosing SLE and accessibility to traditional immunoassays. Type 1 interferon pathway activation is present in most patients with active SLE. Although gene expression assays are not routinely available, detection of interferon-α-dependent expression

of Siglec-1 (sialoadhesin) on peripheral monocytes by flow cytometry permits the rapid assessment of the activation status of the type 1 interferon pathway.[21]

Treatment of extra-renal SLE

Treatment goals

SLE treatment goals must be balanced by taking multiple disease-specific and patient-specific aspects into consideration, especially the individual profile of involved organ manifestations. Although the disease itself can cause severe and irreversible damage, therapeutics such as glucocorticoids or cyclophosphamide can contribute to damage or have substantial toxic effects.[3] Thus, the development of an individual treatment strategy is rather complex with the ultimate challenge to reduce disease activity and prevent damage accrual caused by the disease or its treatment. The achievement of a disease activity state associated with a reduction in organ damage was the impetus behind proposals of the lupus low disease activity state (LLDAS;[22] panel 2) and definition of remission[23] (panel 3). In this regard, there is no evidence that non-steroidal anti-inflammatory drugs or analgesics, as well as most of the conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or immunosuppressives, can prevent organ damage. The optimal outcome should be an improvement in disease activity, prevention of damage and disability, and a reduction in mortality.[24] In this context, belimumab has been shown to reduce damage accrual,[25] consistent with data from a long-term extension study[26] and a study using propensity matching, in which damage accrual in patients taking belimumab was lower than in those on standard therapy.[27]

Overarching treatment principles for extra-renal SLE

The choice of medication to treat extra-renal (general) SLE manifestations, which comprise skin and joint manifestations in more than 80% of patients, is based on a shared decision between the doctor and patient and should aim to reach and maintain a durable remission or low disease activity to prevent subsequent damage.[3,22,23,28] In this context, glucocorticoids should only be used at the lowest possible dose and for the shortest period of time, antimalarials are strongly recommended, and DMARDs are indicated for patients with persistently active SLE or life-threatening disease. Additionally, the presence of comorbidities such as osteoporosis, cardiovascular disease, metabolic syndrome, fibromyalgia, and infections, and their prevention, need consideration. Education regarding ultraviolet (UV) light protection, diet, and pregnancy counselling are additional items in need of discussion (panel 4).

General treatment algorithms in extra-renal SLE

In addition to specific recommendations for lupus nephritis,[31,32] antiphospholipid syndrome,[29] neuropsychiatric SLE,[33] and pregnancy-related issues in SLE,[34] recommendations have been made by EULAR,[4] the Latin American Group for the Study of Lupus (GLADEL),[7] and the British Society of Rheumatology[3] for general SLE management. Those from the British Society of Rheumatology focus on disease activity issues, whereas the contributions from GLADEL provide guidance regarding specific organ involvement. They are complementary and make recommendations on the pharmacological management of various organ manifestations. They address the importance and use of glucocorticoids, antimalarials, DMARDs, immunosuppressants, plasma exchange, belimumab, rituximab, abatacept, low-dose

***Panel 4*: Primary and secondary preventive measures of comorbidities in patients with systemic lupus erythematosus[3,7,29,30]**

Infection prevention

- Immunisation against influenza, *Haemophilus influenzae* type B, and pneumococcus, and administration of other vaccines except live attenuated vaccines (according to national recommendations); immunisation against human papillomavirus in young women for the prevention of cervical cancer
- Primary prophylaxis with co-trimoxazole in patients with a low CD4 cell count (<200 cells per μL) and conventional antibiotic and antifungal prophylaxis in severe neutropenia (<400–500 cells per μL)
  - Early administration of an antimicrobial if an infection develops
  - Consideration of intravenous immunoglobulin in cases of severe hypogammaglobulinaemia (IgG <4 g/L)

Cardiovascular disease prevention

- Arterial: control of traditional risk factors (eg, hyperlipidaemia, arterial hypertension [administration of angiotensin II receptor blockers and angiotensin-converting-enzyme inhibitors], hyperuricaemia, immobility) and cessation of smoking; administration of statins and antimalarials
- Venous: thromboprophylaxis when exposed to additional risk factors (eg, immobility, fracture, hospitalisation, operations) with medical (eg, heparin) and non-medical (eg, stockings) measures
- Avoidance of high-dose glucocorticoids (which enhance arterial and venous risk)
- In patients with coexistent antiphospholipid syndrome: secondary prophylaxis of vascular occlusions using vitamin K antagonists (avoid direct oral anticoagulants)
- In patients with recurrent miscarriage: primary prophylaxis with low-molecular-weight heparin and low-dose aspirin during pregnancy

Fracture and osteoporosis prevention

- Non-pharmacological measures:
  - Exercise and physical therapy, including training of coordination
  - Cessation of smoking, reduction in coffee and alcohol intake, and increase in protein consumption
- Pharmacological measures:
  - Vitamin D supplementation
  - Bisphosphonates or denosumab for at-risk patients
  - Teriparatide and bisphosphonates in patients with fractures
  - Avoidance of high-dose glucocorticoids (>7·5 mg per day), otherwise primary osteoporosis prophylaxis with vitamin D or bisphosphonates for high-risk patients

Skin flare prevention

- Primary and secondary prevention by protecting skin from ultraviolet (UV) light; use of sunscreen and other UV protection measures, also to prevent skin cancers

aspirin, and anticoagulants in the context of induction and maintenance. Despite the existence of recommendations, the creation of a therapeutic regimen is often based on experience of the health professional advocating the treatment, as reflected by a 2015 survey.[35] Treatment algorithms for induction and maintenance are depicted in figure 2.

Therapeutic advances in extra-renal SLE

Drug development has produced numerous drugs that have favourably transformed the lives of patients with rheumatoid and psoriatic arthritis. However, there have been fewer breakthroughs for the SLE community. Despite these shortcomings, the incorporation of immunosuppressive drugs approved for other conditions into the SLE treatment armamentarium (eg, azathioprine, cyclophosphamide, mycophenolate), the approval of a new therapy (belimumab), and the enhanced use of hydroxychloroquine have all contributed to the improved outlook for patients with SLE.

Hydroxychloroquine

Antimalarials are recommended as the standard of care in SLE and should be continued indefinitely. In fact, current dogma is that all patients with SLE should be treated with hydroxychloroquine because of benefits in multiple domains (eg, improvement of rash and arthritis, reduction in risk of early cumulative damage, flare prevention, reduction in lipid concentrations, normalisation of glucose concentrations, anti-thrombotic and anti-atherosclerotic effects, anti-infective characteristics). Antimalarials have also been shown to increase survival,[36] which is possibly related to their effects on lipid and glucose metabolism,[37] their anti-thrombotic and anti-atherosclerotic effects,[38] and their anti-infective potency. An uncontrolled study in 189 patients over 13 years showed that the combined use of hydroxychloroquine and aspirin had primary thromboprophylactic potency that was greater than aspirin or hydroxychloroquine alone.[39] Reduced risk of early cumulative damage and flares has also been documented with hydroxychloroquine[40,41]

Guidelines introduced by the ophthalmology community in 2011 and revised in 2016 not only addressed dosing (previously 6·5 mg/kg and more recently 5·0 mg/kg of actual bodyweight), they also suggested methods and timelines for ocular surveillance.[42] Although physicians debate the optimal dose of hydroxychloroquine, an equally pressing issue is poor drug adherence,[43] which has been assessed by measuring blood concentrations of the drug.[43] If studies reveal that targeting explicit hydroxychloroquine blood concentrations results in improved outcomes, such an intervention should be implemented in clinical practice.

Immunosuppressants

Little data on the efficacy and safety of immunosuppressants in SLE are available from randomised controlled trials (RCTs) or open-label studies. The utility of azathioprine in SLE treatment is based on limited evidence and thus, methotrexate, ciclosporin, and leflunomide could also be considered for patients with SLE[3,7] who require unacceptably high glucocorticoid doses. Low-dose ciclosporin has been shown to be as effective as azathioprine in severe SLE as a steroid-sparing agent,[44] at least for 12 months. In separate studies, leflunomide[45] and methotrexate[46] were more effective than placebo in mild-to-moderately active SLE.

Mycophenolate mofetil was shown to be as effective as cyclophosphamide for extra-renal manifestations in a lupus nephritis study,[47] especially for dermatological and haematological complications. Enteric-coated mycophenolate was evaluated in a multicentre, 24-month RCT of 240 patients with SLE.[48] 120 patients received enteric-coated mycophenolate (target dose 1440 mg per day), and 120 received azathioprine (target dose 2 mg/kg per day) in addition to prednisone or antimalarials (or both). Enteric-coated mycophenolate was superior to azathioprine in terms of clinical remission (ie, a score of 0 according to the Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K]) at 3 and 24 months for at least 8 weeks, British Isles Lupus Assessment Group

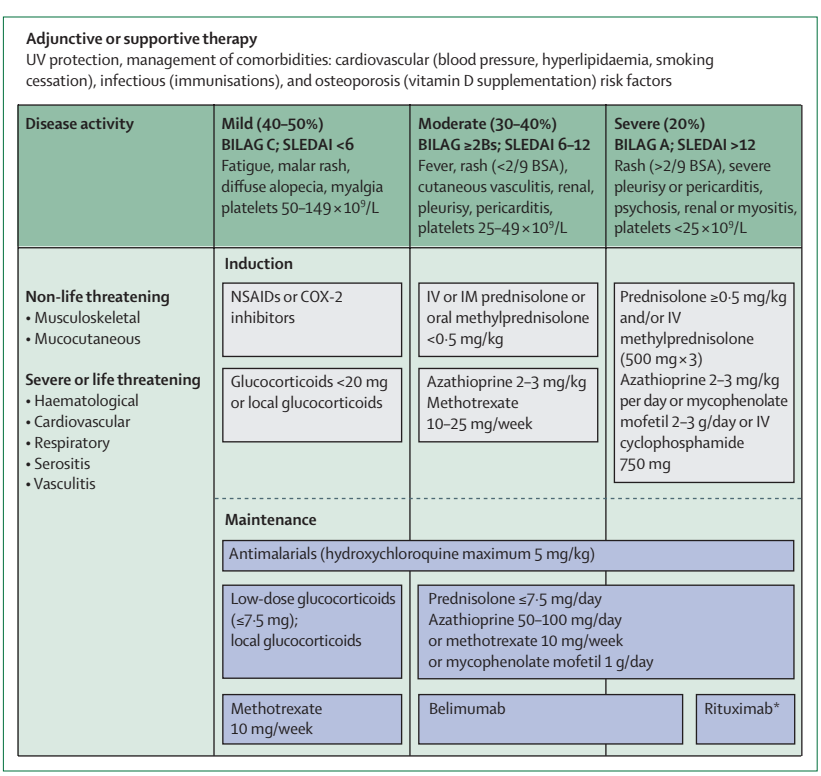

***Figure 2*: Possible treatment algorithms for induction and maintenance in extra-renal systemic lupus erythematosus**

Developed according to the British Society of Rheumatology guidelines for the management of systemic lupus erythematosus in adults.[3] BILAG=British Isles Lupus Assessment Group. BSA=body surface area. IM=intramuscular. IV=intravenous. NSAID=non-steroidal anti-inflammatory drug. SLEDAI=Systemic Lupus Erythematosus Disease Activity Index. UV=ultraviolet. *Still an experimental treatment.

2004 index score, SLEDAI-2K scores at other timepoints, and prevention of increases in glucocorticoid dose. The clinical effects were notable in the renal, mucocutaneous, and haematological domains. The most pronounced therapeutic responses were seen in patients using combined mycophenolate mofetil and antimalarials. Thus, such data have created a far greater appreciation of the value of mycophenolate in extra-renal SLE. Further, the use of mycophenolate in conjunction with other therapies appears to enhance responses. Since mycophenolate mofetil seems to have similar efficacy across different ethnicities or even greater responses in non-white patients,[49] in contrast to other drugs (eg, cyclophosphamide), it evolved as an excellent rescue therapy for active SLE despite the absence of successful registration trials.

Biological therapy in extra-renal SLE

Belimumab

The approval of belimumab (10 mg/kg every 4 weeks) by the US Food and Drug Administration and European Medicines Agency in 2011 was ground-breaking because it was the first time that a drug was approved for SLE following assessment in an RCT.[50,51] Two more belimumab trials were successful, one for the subcutaneous formulation[52] and one undertaken in northeast Asia.[53] Subsequently, studies provided evidence that belimumab substantially delays damage accrual compared with standard of care.[25–27]

Belimumab's favourable effects across different clinical domains[54] might fulfil multitarget therapy principles because it inhibits BAFF, a cytokine of myeloid lineage cells with effects extending beyond the adaptive immune system to cellular components of the innate immune system. Trials are ongoing to evaluate sequential rituximab and belimumab (BLISS-BELIEVE [NCT03312907]; CALIBRATE [NCT02260934], SynBioSe [NCT03747159], and BEAT-LUPUS [ISRCTN47873003]) in extra-renal SLE and lupus nephritis (and in other diseases) to maximise clinical efficacy. Sequential administration of these two biological therapies builds upon observations that B memory cells increase following belimumab treatment. Thus, rituximab following belimumab exposure might more effectively deplete the B-cell compartment than rituximab alone. The reverse administration sequence (rituximab followed by belimumab) is based upon observations of increased BAFF concentrations following B-cell depletion and the concern of an enhanced return of autoreactive B cells in the presence of excessive BAFF concentrations. The CALIBRATE lupus nephritis study, however, did not show a statistical benefit in patients with lupus nephritis at week 48 when belimumab was added to rituximab, cyclophosphamide, and steroids.[55] A third novel tactic, consisting of simultaneous BAFF blockade and B-cell depletion, is under investigation with the monoclonal ianalumab,[56] which targets receptor-bound BAFF (appendix).

Rituximab

Despite the negative findings of the LUNAR[57] and EXPLORER[58] clinical trials in extra-renal SLE and lupus nephritis, respectively, for various reasons,[59] rituximab remains a treatment option for patients with refractory disease. A European survey revealed that 0·5–1·5% of all patients with SLE have taken rituximab.[60] A single centre study[61] reported remarkable responses (90% complete or partial responses) in patients with lupus nephritis, in which oral steroids were avoided during the first 6 months, suggesting that anti-CD20 might have value in early disease. Thus, there is growing sentiment that rituximab is a valuable therapeutic for early and refractory lupus nephritis, adding to its position as a treatment for autoimmune cytopenias. Lupus nephritis is under study with obinutuzumab,[59] a third-generation humanised type 2 anti-CD20 antibody.

Treatment of lupus nephritis

Treatment goals

The preservation of quality of life through the achievement of clinical improvement during a 6–12 month induction phase followed by a maintenance phase that prevents further organ damage is the goal of lupus nephritis treatment. Joint recommendations for lupus nephritis treatment have been published by EULAR and the European Renal Association–European Dialysis and Transplant Association[31] and the ACR[32] (figure 3).

A return to pre-nephritic flare creatinine clearance is the goal. However, given the extraordinary reserve of the kidneys, most patients with new-onset proliferative lupus nephritis maintain normal renal function. Therefore, clinicians rely on proteinuria as a key indicator of disease activity and response to intervention. Achievements in the field of lupus nephritis have been made in prediction of response. Two independent studies (MAINTAIN[64] and Euro-Lupus Nephritis Trial[65]) showed that reductions in proteinuria below 0·7 g per day or 0·8 g per day within 1 year had a high positive predictive value (PPV) for maintaining serum creatinine of 1 mg/dL or less at 7 years (PPV 94%) but a low negative predictive value of 31%.[64] This independently validated biomarker is superior to urinalysis or renal function for the prediction of outcome. However, the value of a proteinuric response has been challenged by Malvar and colleagues,[66] who observed that 50% of their treated lupus nephritis cohort with complete renal responses had a histological activity score of greater than 3 on a repeat biopsy using the National Institutes of Health (NIH) activity index.

Histological classification

Limitations of the ISN–RPS classification of lupus nephritis have been recognised, since they rely mainly on light microscopy, overlook the underlying pathophysiology, and neglect the latest insights into renal molecular signatures. A proposal for the reclassification of lupus nephritis was put forward by Bajema and

See Online for appendix

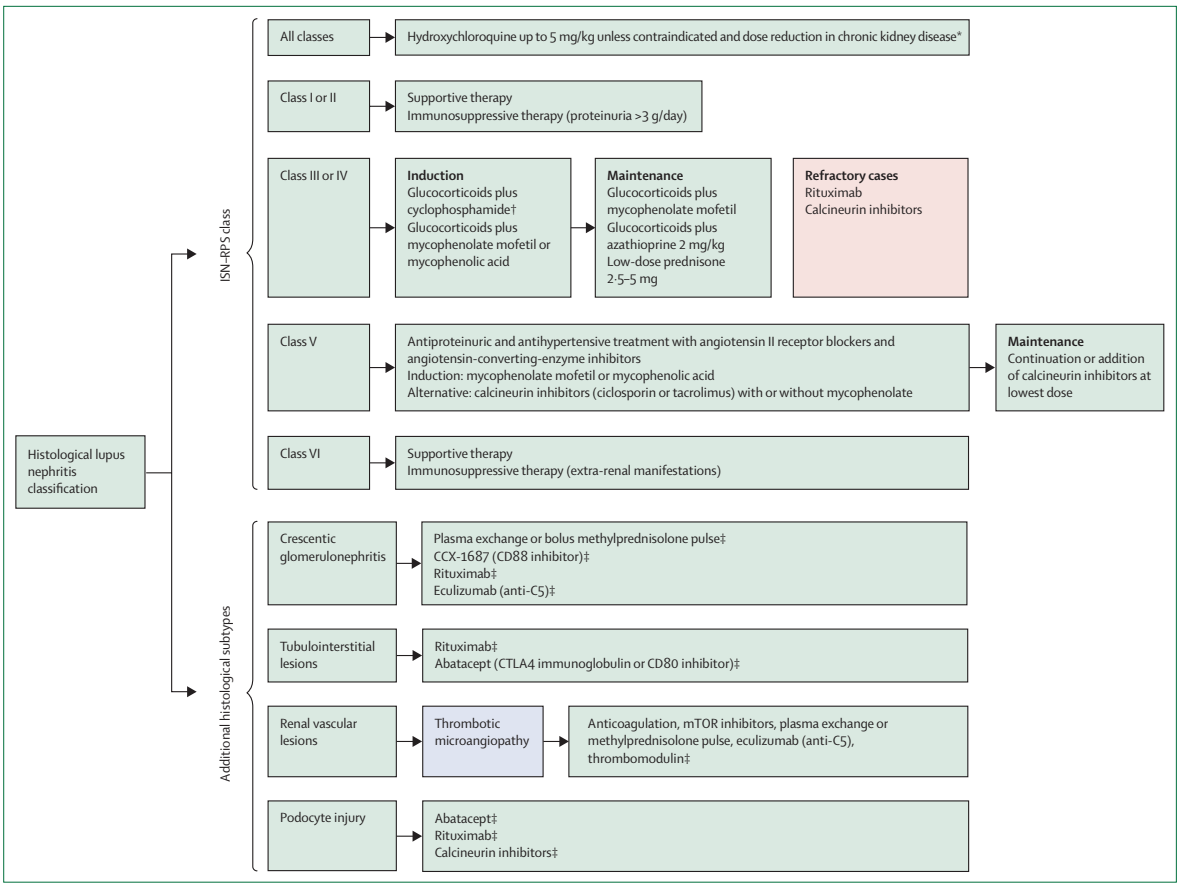

***Figure 3*: Proposed treatment algorithm for established and suggested pathological subtypes of lupus nephritis**
The treatment algorithm for established pathological subtypes (ISN–RPS classes I–VI) is based on recommendations from the Joint European League Against Rheumatism (EULAR) and European Renal Association–European Dialysis and Transplant Association,[31] American College of Rheumatology,[32] the 2019 update of EULAR recommendations,[28] and the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.[62] The treatment algorithm for the suggested pathological subtypes of lupus nephritis is based on a treatment algorithm proposed by Yu and colleagues,[63] adapted by permission of Springer Nature. ISN=International Society of Nephrology. RPS=Renal Pathology Society. mTOR=mechanistic target of rapamycin. *According to the 2019 update of EULAR recommendations.[28] †Dose of six pulses every 2 weeks at a fixed dose of 500 mg as recommended by the Euro Lupus Nephritis Trial. ‡Still at trial stage; efficacy unknown.

colleagues in 2018.[67] They provided new definitions for mesangial hypercellularity and for cellular, fibrocellular, and fibrous crescents. They proposed elimination of the term endocapillary proliferation and the removal of the class IV-S and IV-G subdivisions of class IV lupus nephritis. They suggest that activity and chronicity indices should be applied to all classes and should replace the A and C designations for proliferative nephritis. Fibrinoid necrosis, podocyte injury, tubulointerstitial lesions in the presence or absence of fibrosis, and renal vascular lesions (thrombotic microangiopathy) will receive attention in the new classification, which is currently the subject of scientific discussions (figure 3). Identification of interstitial lesions has been considered a key prognostic factor for end-stage renal disease and as such requires assessments beyond the glomeruli.

Induction treatment in lupus nephritis

The induction phase of lupus nephritis treatment refers to the initial phase of therapy when an aggressive regimen is initiated. Although quite arbitrary, the duration of induction therapy is generally 6–12 months. For induction of proliferative lupus nephritis (ISN–RPS classes III and IV lupus nephritis), the Euro-Lupus Nephritis Trial regimen of low-dose cyclophosphamide (six pulses every 2 weeks at a fixed dose of 500 mg; figure 3) yielded similar outcomes as the NIH high-dose regimen (750 mg/m² monthly then every 3 months).[65] In the pursuit of safer and equally effective therapies, mycophenolate mofetil was studied. Despite mycophenolate not achieving regulatory approval for lupus nephritis, several studies showed equivalence of mycophenolate mofetil to cyclophosphamide for lupus nephritis induction.[68] Racial differences in induction responses were evident, with mycophenolate mofetil showing similar or slightly greater responses in black or mixed-race patients than in white patients, whereas cyclophosphamide was shown to be more potent in white individuals than in black or mixed-race individuals.[68]

Typical mycophenolate mofetil induction doses range from 2·0 g to 3·0 g daily depending on race, with white patients and black patients targeted for the highest doses and Asian patients receiving lower than maximal doses. Doses are reduced by 33–50% during long-term maintenance. Meta-analyses have shown superiority of mycophenolate mofetil and calcineurin inhibitors (including their combination) over cyclophosphamide with regard to treatment response.[69–71]

Maintenance treatment in lupus nephritis

For maintenance, mycophenolate mofetil and azathioprine remain treatment options (figure 3). In a key study published in 2004, Contreras and colleagues[72] showed that patient survival was better and chronic renal impairment less frequent when azathioprine or mycophenolate mofetil was used instead of quarterly pulses of intravenous cyclophosphamide as maintenance. Subsequently, two RCTs[49,73] compared mycophenolate mofetil with azathioprine as maintenance therapy. The 3-year maintenance phase of the Aspreva Lupus Management Study[49] yielded a 50% reduction in treatment failure (defined as death, end-stage renal disease, doubling of the serum creatinine concentraion, renal flare, or the need for rescue therapy) in patients treated with mycophenolate mofetil versus azathioprine. However, superiority of mycophenolate mofetil to azathioprine was not shown in the MAINTAIN Nephritis Trial for the first 5 years[73] or in the 10-year follow-up using a composite index consisting of absence of end-stage renal disease, all renal flares, and proteinuric and nephritic flares.[74] However, a meta-analysis found that mycophenolate mofetil was superior to azathioprine in preventing flares during maintenance.[71]

Alternative therapeutic regimens

Calcineurin inhibitors

Calcineurin inhibitors, which belong to a group of immunosuppressive agents that block T-cell activation through suppression of the calcium and calcimodulin-dependent phosphatase calcineurin, have undergone a renaissance. The use of calcineurin inhibitors in lupus nephritis has been recommended for refractory cases of class III or IV lupus nephritis (figure 3),[31,32,62] but their use is limited to 6 months for induction. Agents such as ciclosporin and tacrolimus have long been used in organ transplantation. Ciclosporin binds to cyclophilins and tacrolimus binds to FKBP12. They both inhibit calcineurin activity and prevent nuclear translocation of transcription factors, such as the NFAT transcription factors, which are involved in interleukin (IL)-2 gene transcription.[75] Calcineurin inhibitors inhibit T-cell-mediated immune responses and stabilise podocytes, protecting against podocytopathy and proteinuria. The side-effects of calcineurin inhibitors—ie, increased infection risk, hirsutism, hypertension, hyperlipidaemia, and gingival hyperplasia—are less frequent with tacrolimus than with ciclosporin. Acute toxic effects of calcineurin inhibitors (eg, neurotoxicity, diabetogenicity, and acute nephrotoxicity) can usually be minimised by monitoring and adjusting drug doses. Chronic calcineurin inhibitor nephrotoxicity (progressive loss in glomerular and tubular function) is lower with tacrolimus than with ciclosporin because of the lower vasoconstrictive and fibrogenic potential of tacrolimus. However, no evidence exists on the incidence of chronic calcineurin inhibitor nephrotoxicity in lupus nephritis and its relationship to systemic exposure and residual SLE activity in the kidneys.[75]

An RCT in 150 Chinese patients with active lupus nephritis (RPS–ISN class III or V) compared tacrolimus (0·06–0·1 mg/kg per day) with mycophenolate mofetil (2–3 g per day) in combination with prednisolone (0·6 mg/kg per day for 6 weeks and tapered).[76] After 6 months on mycophenolate mofetil, 59% of patients had achieved a complete renal response, 21% had a partial renal response, and 20% had no response, compared with 62% with complete response, 27% with partial response, and 11% with no response in the tacrolimus group. After switching to azathioprine for maintenance, the proportion of patients who had proteinuric or nephritic renal flares was numerically higher (but not significantly higher) in tacrolimus-treated patients after mean of 60·8 months (SD 26). The cumulative incidence of a composite outcome consisting of a decline in creatinine clearance by 30% or greater, development of chronic kidney disease stage 4 or 5, or death was similar in both treatment groups (21% with mycophenolate mofetil *vs* 22% with tacrolimus).

Calcineurin inhibitors can also be used for maintenance therapy. EULAR and ACR guidelines recommend azathioprine or mycophenolate mofetil as optimal maintenance therapy after successful induction. However, calcineurin inhibitors might offer similar efficacy, but potential side-effects could influence the decision about whether to use them. An Italian RCT compared ciclosporin (2·5–3·0 mg/kg per day) to azathioprine (2 mg/kg per day) for maintenance of remission in patients with lupus nephritis after induction treatment with high-dose glucocorticoids and oral cyclophosphamide.[77] At 4 years, the proportion of patients with renal flares was not significantly different between the two groups (19% with ciclosporin *vs* 24% with azathioprine). One study in Chinese patients reported similar proportions of patients with renal flares between tacrolimus (target serum concentration 4–6 ng/mL) and azathioprine (2 mg/kg per day) as maintenance therapy in 70 patients with lupus nephritis.[78] In the CYCLOFALUNE trial,[79] a similar proportion of patients on ciclosporin achieved a response to those on conventional cyclophosphamide treatment over 7·7 years, whereas a meta-analysis[80] showed that tacrolimus was more effective than cyclophosphamide at inducing complete remission in class III and IV lupus nephritis.

Besides azathioprine, tacrolimus represents an option for young patients with lupus nephritis who want to preserve fertility and in those who are refractory or intolerant to mycophenolate mofetil, cyclophosphamide, or azathioprine. In contrast to cyclophosphamide and mycophenolate mofetil, tacrolimus is relatively safe and effective in treating lupus flares during pregnancy, and excretion of tacrolimus in breast milk is negligible.[81]

In patients who have renal impairment, titration of the dose of tacrolimus can be challenging and require drug level monitoring. There is no evidence that the trough concentration of tacrolimus correlates with clinical efficacy in lupus nephritis.[76] When calcineurin inhibitors are used as long-term maintenance therapy for SLE, the lowest effective dose should be used, and close monitoring of renal function, blood pressure, glucose and lipid concentrations, and drug concentrations is mandatory.

Multitarget therapy

The inclusion of calcineurin inhibitors in conjunction with other medications (especially mycophenolate mofetil) provided the foundation of the multitarget therapy strategy in lupus nephritis. Combinations of immunosuppressive agents with different mechanisms of action can achieve synergism and facilitate the use of lower doses of individual drugs leading to potential safety advantages. Experience with calcineurin inhibitors in patients undergoing renal transplantation served as the impetus to apply this approach to lupus nephritis treatment. The first such study[82] evaluated multitarget therapy (tacrolimus 4 mg per day plus mycophenolate mofetil 1 g per day) versus cyclophosphamide in 368 patients with lupus nephritis for induction (24 weeks). Complete responses occurred in 46% of patients on multitarget therapy versus 26% on cyclophosphamide 0·5–1·0 g/m² (p<0·001). Notably, serious infections were more common in the mycophenolate mofetil plus tacrolimus group, as were withdrawals due to pneumonia or herpes zoster infection. Responders entered maintenance on continued multitarget therapy or were switched from cyclophosphamide to azathioprine. The differences between groups were less striking at 18 months: the proportion of patients who relapsed was 5·5% with multitarget therapy versus 7·6% with azathioprine. More patients had adverse events (44·4%) and discontinuations (8·9%) on azathioprine than with multitarget therapy continuation (16% and 1·7%, respectively).[83] Combined low-dose tacrolimus and mycophenolate mofetil has the potential to improve proteinuria in two-thirds of patients with lupus nephritis without the need for glucocorticoids.[75]

The data so far indicate that multitarget therapy might have value in the induction phase for 6 months, whereas its superiority is less clear for maintenance. Overall, the simultaneous targeting of several key nodes of immune activation[59] holds promise given the biological and clinical heterogeneity of SLE. A remaining challenge to understand the efficacy–safety balance of multitarget therapy is to identify optimal doses of individual multitarget therapy components versus simply combining conventional doses.

Renal transplant in lupus nephritis

A similar transplant outcome to patients without SLE has been shown retrospectively, together with a superiority of renal transplantation over dialysis in terms of patient survival (relative risk ranged from 0·19 to 0·32).[31] Although the overall transplant survival in lupus nephritis is similar to other renal transplants,[84] it is worse if antiphospholipid syndrome is present,[85] indicating the pathogenic importance of coexistent thrombotic microangiopathy (appendix).

Comorbidities and adjunctive therapies

Primarily because of comorbidities, patients with SLE have a five times greater risk of mortality compared with the general population. Although differentiation between disease-related and treatment-related morbidity is difficult, there is evidence that patients with SLE have increased infectious, arterial (cardiovascular and cerebrovascular) and venous (typical and atypical), metabolic, osteoporotic, and malignancy complications (non-Hodgkin lymphoma, lung cancer, and hepatobiliary cancer). Consensus recommendations[3,4,7,31,28] provide guidance on how to manage these comorbidities; however, they mainly follow common clinical practice (panel 4). Although the use of sunscreens for UV light protection in patients with SLE is supported by a double-blind trial,[86] low-dose aspirin use in patients with associated anti-phospholipid antibodies to prevent thrombosis or osteoporosis prophylaxis[30] is not based on specific evidence for patients with SLE, but should still be considered (figure 2). Similarly, weight control, vaccinations, physical exercise, and smoking cessation are indicated, especially in patients with increased cardiovascular risk. Statins and antihypertensive therapy might be required for some patients. The broad effects of antimalarials beyond their anti-inflammatory properties and their association with increased survival justify their use in all patients with SLE.[87] Demonstration of reduced damage accrual and reduction of comorbidity risk factors (eg, infections, hypertension, dyslipidaemia, atherosclerosis, coronary heart disease, and osteoporosis) can only be captured by long-term follow-up studies.

The quest to spare steroids

Restricting steroid exposure poses a formidable challenge to both patients and clinicians. Treat-to-target recommendations aim for the "lowest glucocorticoid dosage needed to control disease, and, if possible, glucocorticoids should be withdrawn completely".[88] A meta-analysis of 28 studies showed that most studies of drugs (eg, belimumab, tabalumab, epratuzumab) in SLE showed

steroid-sparing effects compared with placebo (pooled risk ratio 1·36; p=0·67).[89] Although only studies of belimumab were successful, these data show that glucocorticoid sparing is a feasible endpoint. Independently, cumulative damage by glucocorticoid burden has been shown, particularly for cataract development and osteoporosis.[90] Zahr and colleagues[91] examined predictors of steroid tapering in patients in the Hopkins Lupus Cohort. They documented an increase in tapering of prednisone to below 5 mg daily in the modern era, which is encouraging.[92,93]

Novel treatment strategies and outcome measures

Treat to target, lupus low disease activity, and remission in SLE

Successful treat-to-target strategies have improved outcomes for patients with diabetes, hypertension, or rheumatoid arthritis. Adapting a similar approach, initiatives in SLE have defined treatment goals, which range from an operational definition of LLDAS[22] (panel 2) to remission definitions (panel 3).[23,94] They serve multiple purposes, chief of which is the association with diminished damage accrual and mortality.

LLDAS in SLE[22,95] has been associated with reduced damage accrual. The definition of remission in SLE (known by its acronym DORIS)[23] and a simultaneous proposal by Zen and colleagues[94] (known as the Doria proposal, named after one of its principal authors) considered the complexity of SLE, taking into account four pillars: clinical disease activity, serological activity, treatment modalities, and durability. In terms of treatment, antimalarials and prednisolone at a dose of 5 mg per day or lower do not exclude the attainment of remission on therapy. Although both proposed remission definitions considered that remission in SLE is a durable state, the two definitions differ slightly, in that the Doria definition did not include the patient's global assessment and distinguished between patients on and off glucocorticoids.

Durable remission is a laudable goal, but studies have shown that the achievement of such a state is highly variable depending on the specific definition of remission and the cohort that was analysed.[96] Retrospective analyses have suggested that LLDAS might have value as an outcome in clinical trials. Research is evaluating the utility of LLDAS and remission as outcomes for clinical trials and clinical practice, including their potential to inform on long-term damage accrual.[90]

Experimental therapies: eclectic and innovative strategies

Despite the availability of multiple therapies, the proportion of patients with a response in the standard-of-care groups of extra-renal and lupus nephritis clinical trials has been unacceptably low (<50% and <40%, respectively).[3,7] Although the study populations might not have been representative of patients in community practices, more effective and safer therapies are urgently needed.

Clinical trial activity in SLE has been unprecedented, with many pharmaceutical companies recognising this urgent need for safer and more effective therapies (appendix). The approaches being taken are as eclectic as the disease itself. However, drug development has been particularly challenging, with a large number of phase 2 and 3 clinical trials not meeting their primary endpoints.[59,97,98] Reasons are manifold, including inappropriately defined target populations (rituximab seems to be effective in otherwise refractory patients[60] or new-onset lupus nephritis[61]), study design (including outcome measures and improper glucocorticoid-sparing strategies), and possibly ill-defined targets.

Various approaches exploiting extracellular and intracellular targets are in clinical development, such as anti-cytokine targeting, new cellular approaches (ie, mesenchymal stem-cell transplantation), blocking of co-stimulation and enhanced B-cell depletion, blocking of intracellular signalling pathways, and immmunomodulatory concepts (ie, low dose IL-2 therapy), among others. As a result of the many approaches being explored, the number of drugs in development is huge, so rather than list them all, we discuss here the key late-stage development programmes and strategies.

Voclosporin

Voclosporin, in clinical development, is an analogue of ciclosporin with stronger binding capacity and greater calcineurin inhibition. It is expected to have increased potency, faster elimination, and less plasma variability than ciclosporin.[75] In a phase 2b RCT (AURA),[99] 265 patients with active lupus nephritis (RPS–ISN class III, IV, or V) were randomly assigned to receive one of two doses of voclosporin (23·7 mg twice a day or 39·5 mg twice a day) or placebo in addition to glucocorticoids and mycophenolate mofetil (2 g per day). At week 24 and under strict glucocorticoid tapering, the low-dose voclosporin group had significantly higher complete (33% in the low-dose voclosporin group *vs* 19% in the placebo group) and partial (70% *vs* 49%) renal responses than the placebo group. At week 48, complete responses occurred in 49% of patients (p<0·001 *vs* placebo) treated with low-dose voclosporin, 40% (p=0·026 *vs* placebo) on high-dose voclosporin, and 24% on placebo, whereas partial renal responses occurred in 69% (p=0·007) on low-dose voclosporin, 72% (p=0·002) on high-dose voclosporin, and 48% on placebo. Proportions of patients with serious adverse events and mortality, however, were numerically higher in the voclosporin plus mycophenolate mofetil combination groups. Deaths occurred in 1% of patients on placebo, 11% of those on low-dose voclosporin, and 2% of those on high-dose voclosporin. A phase 3 study of voclosporin in lupus nephritis has completed enrolment (NCT03021499).

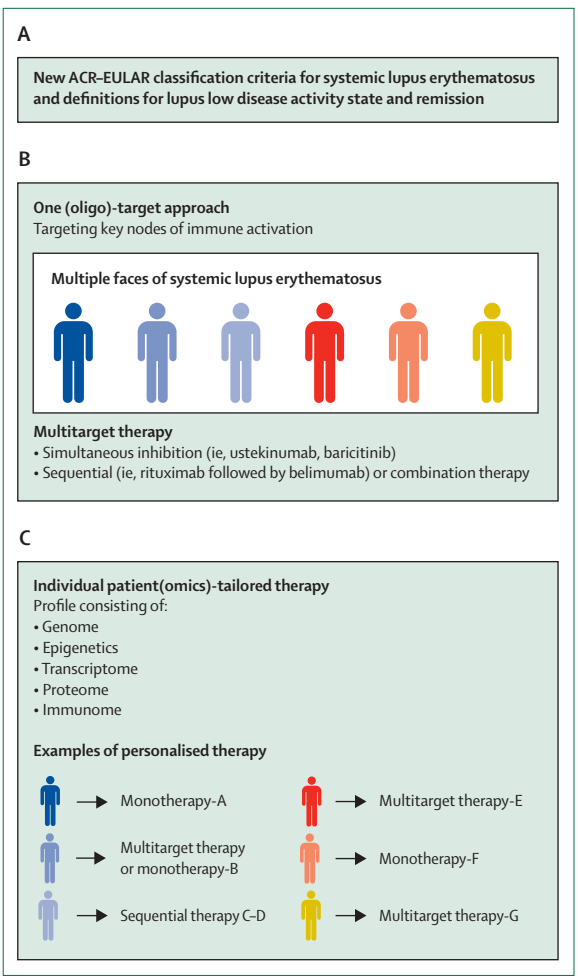

***Figure 4*: Concepts to improve therapeutic outcomes in systemic lupus erythematosus**
We propose that improved classification and outcome definitions (A) and multitarget therapy concepts (B) must be mandated before individualised therapy becomes a reality (C). ACR=American College of Rheumatology. EULAR=European League Against Rheumatism.

Type 1 interferon inhibition

A unique SLE strategy is to target type 1 interferons, given the prominent role that they appear to play in SLE pathogenesis and the presence of a type 1 interferon signature in most patients with SLE. Monoclonal antibodies that inhibit interferon-α alone (sifalimumab,[100] rontalizumab[101]) were first evaluated in phase 2 RCTs, but anifrolumab, which inhibits the type 1 interferon receptor (IFNAR) and hence all type 1 interferons, was found to be far superior to placebo in phase 2 trials in patients with extra-renal disease.[102] Another strategy to suppress the interferon pathway is vaccination with interferon alfa kinoid.[103] Production of type 1 interferon along with other cytokines and chemokines can be reduced with agents that target plasmacytoid dendritic cells. This reduction in type 1 interferon has been accomplished with BCL2 inhibitors, a cytolytic antibody directed against IL-3Ra, and BIIB059 (a non-cytolytic antibody that binds BDCA2 [CLEC4C]; appendix). Although the rationale to block type 1 interferons is very convincing, enthusiasm has been rebalanced since one anifrolumab phase 3 study did not achieve its primary endpoint.[104] However, as with all SLE trials with negative findings, the issue is whether the drug, trial design, or outcome measures are at fault.

BTK inhibition

Studies with second-generation BTK inhibitors, such as evobrutinib or GDC053, are underway.[59] These compounds probably have multiple effects on B cells (appendix) and also macrophages. Evobrutinib has been efficacious in relapsing remitting multiple sclerosis, a disease that also responds to anti-CD20 therapy.

Applying past lessons learned to future drug development

Single target approaches with inhibitors, such as anti-CD20, anti-interferon-α, anti-IL-6, or anti-IL-6 receptor antibodies, CTLA4 immunoglobulin targeting CD80 and CD86, or anti-CD22 antibody (epratuzumab), possibly have been too restricted in their effects given the multitude of active pathways in a disease as heterogeneous as SLE. In transitioning from phase 2 to phase 3 clinical trials, more molecular investigation needs to occur to identify baseline predictors of response before assembling a phase 3 protocol. For example, anifrolumab 300 mg yielded an effect size at week 52 of 32·3% (absolute difference from placebo) in the patients with a high type 1 interferon signature at baseline, which was greater than in those with low interferon at baseline (7·7%,).[102] The so-called baseline enhanced responder profile to belimumab (ie, SLEDAI score ≥10, anti-dsDNA positive, low complement concentrations, and increased glucocorticoid use), however, was not identified until after phase 3 data[105] became available. Several companies advanced to phase 3 studies despite the absence of phase 2 data, having relied on rheumatoid arthritis data (for rituximab, ocrelizumab, tabalumab, abatacept). The future of SLE classification is very likely to transition from clinical phenotypes to molecular phenotypes, and this changeover should facilitate the identification of patients appropriate to receive particular targeted therapies.

We put forward the hypothesis that SLE would be best addressed by strategies that cover multiple therapeutic targets (multitarget therapy; figure 4). This strategy can either be achieved by sequential therapy, combinations of drugs, or pluripotent compounds. For example, pluripotent glucocorticoids and approaches using proteasome inhibitors, which have effects that extend beyond plasma cells,[106,107] might fall into this category. Two programmes with phase 2 data support this idea. A study in extra-renal SLE of ustekinumab, which targets IL-12 and IL-23 and is approved for

other indications, found that 62% of patients had an Systemic Lupus Erythematosus Responder Index-4 response at week 24 compared with 33% in the placebo group.[108] The effect size together with the known safety profile hold promise for a favourable result in an upcoming phase 3 study. Combined inhibition of type 2 interferons and IL-17 represent a plausible rationale (appendix).

Another study evaluated the JAK1 and JAK2 inhibitor baricitinib in SLE[109] at doses of 2 mg and 4 mg versus placebo for 24 weeks. The primary endpoint, the proportion of patients achieving resolution of arthritis or rash according to SLEDAI-2K, was achieved by significantly more patients (67%) treated with 4 mg than those given placebo (48%), whereas the 2 mg treatment (51% response) was not significantly different to placebo. Safety findings were similar to data known for rheumatoid arthritis. This compound interferes with various proinflammatory pathways, such as type 1 and 2 interferons, IL-6, IL-12, Il-23, and the common γ-chain cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21). Apart from multitarget therapy concepts, this study, which benefited patients treated with baricitinib with rash and arthritis, is an example of another strategy to address SLE heterogeneity (panel 1) because it focused on specific organ manifestations to study more homogeneous patient populations. A similar approach is to investigate patients with identical biomarkers (ie, type 1 interferon signature). The future will reveal if one or the other, or both, will ensure success.

The concept of rebalancing the immune system in contrast to intervening with harsh immunosuppression is extremely appealing. Early phase trials[110,111] with low dose IL-2 have reported clinical responses and increases in regulatory T cells. Together with the known IL-2 deficiency in SLE, various compounds using different mechanisms (appendix) to mimic IL-2 effects are in clinical studies to pursue this line of evidence.

Conclusions

The future for patients with SLE is bright. The disease is being attacked from all sides to gain better insights so that remission is a possibility for more patients, and morbidity and mortality are greatly reduced. These goals will be achieved through the broad efforts of basic, translational, and clinical scientists, clinicians, patients and their families, allied professionals, and everyone engaged in the lupus community.

Contributors

Both authors developed the manuscript on the basis of the literature research, and edited, revised, read, and approved the final manuscript including display items.

Declaration of interests

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