A glimpse into the future of systemic lupus erythematous

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Abstract: This viewpoint article on a forecast of clinically meaningful changes in the management of systemic lupus erythematosus (SLE) in the next 10 years is based on a review of the current state of the art. The groundwork has been laid by a robust series of classification criteria and treatment recommendations that have all been published since 2019. Building on this strong foundation, SLE management predictably will take significant steps forward. Assessment for lupus arthritis will presumably include musculoskeletal sonography. Large-scale polyomics studies are likely to unravel more of the central immune mechanisms of the disease. Biomarkers predictive of therapeutic success may enter the field; the type I interferon signature, as a companion for use of anifrolumab, an antibody against the common type I interferon receptor, is one serious candidate. Besides anifrolumab for nonrenal SLE and the new calcineurin inhibitor voclosporin in lupus nephritis, both of which are already approved in the United States and likely to become available in the European Union in 2022, several other approaches are in advanced clinical trials. These include advanced B cell depletion, inhibition of costimulation via CD40 and CD40 ligand (CD40L), and Janus kinase 1 (Jak1) and Tyrosine kinase 2 (Tyk2) inhibition. At the same time, essentially all of our conventional therapeutic armamentarium will continue to be used. The ability of patients to have successful SLE pregnancies, which has become much better in the last decades, should further improve, with approaches including tumor necrosis factor blockade and self-monitoring of fetal heart rates. While we hope that the COVID-19 pandemic will soon be controlled, it has highlighted the risk of severe viral infections in SLE, with increased risk tied to certain therapies. Although there are some data that a cure might be achievable, this likely will remain a challenge beyond 10 years from now.

Keywords: B cell depletion, calcineurin inhibition, classification criteria, costimulation blockade, diagnosis, interferon receptor blockade, lupus nephritis, quality of life, recommendations, systemic lupus erythematosus, therapy

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Before taking on the challenge of trying to look into the future of managing patients with systemic lupus erythematosus (SLE), it is useful to start by examining the current state of the art. From its origins as an often deadly, mysterious disease, SLE has become a chronic condition, in which quality of life and comorbid complications have replaced inflammation as the greatest challenges in management for most patients.\textsuperscript{1–3} The use of cyclophosphamide for organ-threatening disease has been reduced in scope, dose, and length, and mycophenolate is an established alternative option for many patients with severe disease.\textsuperscript{4–8} In addition to antimalarials, azathioprine (approved in Europe), and glucocorticoids, belimumab, a monoclonal antibody against the B cell cytokine B lymphocyte stimulator (BLYS)/B cell activating factor (BAFF), was initially approved for the treatment of nonrenal lupus 10 years ago.\textsuperscript{9–11} The belimumab trials also became models for successfully testing new drugs for nonrenal SLE in randomized clinical trials, with one additional therapy...
Several international projects over the last few years have documented progress in SLE clinical care. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2019 classification introduced positive antinuclear antibodies (ANA) as an obligatory entry criterion, grouped items in weighted organ domains, and replaced individual exclusion criteria with one attribution rule, that items should only be counted if there is no more likely explanation than SLE. The updated EULAR recommendations clearly described important developments in the management of SLE, including the use of hydroxychloroquine in every SLE patient without contraindication, and the importance of risk factor modification, treating to target, and minimization of glucocorticoid exposure.3 The Latin American Grupo Latino Americano de Estudio del Lupus (GLADEL) recommendations expressed the same viewpoints regarding antimalarials for all SLE patients and keeping glucocorticoid doses low.

The EULAR/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) recommendations for lupus nephritis redefined treatment goals based on accumulating data that proteinuria levels of not more than 0.5–0.7 g/day – or a corresponding urine protein/creatinine ratio of 0.5–0.7 g/g creatinine – is most predictive of good long-term kidney outcome. These guidelines also emphasize the importance of kidney biopsy and of renin-angiotensin-aldosterone system (RAAS) blockers and other nonimmunological renoprotective therapeutic strategies in managing lupus nephritis. EULAR guidelines on antiphospholipid syndrome (APS) provide practical guidance in treating this condition associated with SLE, including the lack of efficacy of direct oral anticoagulants (DOACs) in APS. Novel APS classification criteria are currently in development.

After multiple disappointments, which included negative trials of the costimulation blocker abatacept, the anti-CD22 antibody epratuzumab, the anti-interferon-α (IFNα) antibody rontalizumab, the anti-interleukin-12 (IL-12)/IL-23 antibody ustekinumab and the Bruton’s tyrosine kinase inhibitor fenebrutinib, we have recently seen several positive phase III trials and regulatory approvals for nonrenal SLE and lupus nephritis. These include the anti-interferon receptor antibody anifrolumab for nonrenal SLE, as well as belimumab and the new calcineurin inhibitor vocolsporin for lupus nephritis.

These successes provide a solid foundation for the further development of targeted therapies in nonrenal SLE and lupus nephritis.

**Toward more fully understanding the pathogenesis of SLE**

The EULAR/ACR criteria are conventional classification criteria, based on clinical manifestations and a few immunological parameters, namely ANA, antibodies to double-stranded DNA (dsDNA), Sm, and phospholipids, and complement C3 and C4, which were already part of the Systemic Lupus International Collaborating Centers (SLICC) criteria and, with the exception of complement proteins, the ACR 1997 revised criteria. In parallel, important polyomics projects were ongoing, which examined classification from a molecular standpoint across autoimmune diseases. The lupus community debated whether the overarching concept of SLE as a singular disease would survive. We indeed have two competing models of SLE, namely as one disease entity whose specific features are influenced by other variations in the composition of the individual’s immune system and environment versus a syndrome comprising several more clearly distinct pathogenic entities (Figure 1).

The results of the EULAR/ACR classification criteria project are compatible with the idea that SLE will remain one disease entity. The underlying clinical argument comes from an exercise on associations between SLE organ manifestation items. This analysis became necessary because of the hypothesis that some SLE manifestations and immune biomarkers might cluster more frequently together, forming ‘buckets’, which would already be close to subdividing SLE into several diseases. The implication of such associations would be that items were not independent of each other, a problem in classification.

The results gave an answer that was only partly expected: yes, there were associations, but only within organ domains, such as between mucocutaneous manifestations, between hematological manifestations, and, serologically, between SLE-specific antibodies and between antiphospholipid antibodies. Between different organ domains, however, no associations could be detected. These
findings led to structuring the EULAR/SLE criteria into organ domains, and also suggest that various organ manifestations, caused by diverse molecular mechanisms, can combine in heterogeneous ways in an individual.

When interpreting SLE as a single entity, polyomics data are helpful in defining factors that increase SLE susceptibility as well as factors that modulate disease and are therefore important for therapeutic strategies. It is well-established that large proportions of the genetic polymorphisms in SLE are shared among other autoimmune diseases. While the twin concordance rate in SLE is likely around 25%, and certainly not above 50%, SLE patients frequently have close relatives with other, more common autoimmune diseases. Monogenic SLE traits are usually linked to one of three mechanisms, namely a reduced capability of removing remnants of dead cells (such as in C1q deficiency), constant type I interferon production (such as in TREX1 mutations) and B cell hyperactivity.31–33

These factors intuitively make sense for a disease that is clinically characterized by the consequences of a wide variety of different autoantibodies, which typically include antibodies to DNA or RNA and to DNA-binding and RNA-binding proteins, such as histones, Sm, U1RNP, Ro, or La.34 These antigens are found in remnants of dead cells and can be presented to the immune system if apoptotic or other dying cells are not removed.35 Furthermore, while type I interferons have numerous antiviral and immunostimulatory effects, prominent among them is promotion of B cell differentiation into antibody-producing cells, which is also evident during B cell repopulation after rituximab therapy.36,37

However, recent work in the area of type I interferon has presented an alternative or complimentary view of SLE pathogenesis. In the setting of a viral infection, plasmacytoid dendritic cells (pDCs) are the predominant circulating cell source of type I interferon, and this was assumed to be the situation in SLE as well. However, pDC numbers and immunogenic functions are now known to be markedly impaired, not only in patients with SLE, but in all ANA-positive individuals, even in the absence of organ inflammation or therapy.38 Instead, and even in ANA-positive healthy individuals, nonhematopoietic sources of type I interferon, such as from keratinocytes in the skin, may

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**Figure 1.** SLE pathogenesis and SLE as a disease entity or a syndrome. Polyomics studies suggest different molecular clusters. These findings can be interpreted in two ways. These can all be viewed as distinct disease entities, which together form a syndrome, namely SLE. Alternatively, SLE can be viewed as one disease entity, and the molecular clusters as the makeup of the immune system that leads to differences in disease pathophysiology (on the inflammatory level).
predominate.\textsuperscript{38} That finding is corroborated by studies in established cutaneous lupus.\textsuperscript{39,40} Since the stromal cells of all organs affected by SLE are capable of producing and responding to type I interferons, this suggests a novel model of pathogenesis in which ‘target organs’ in fact play an active role in the initiation and propagation of inflammation. This hypothesis, interferons of non-hematopoietic origin playing a major role, may help to explain why such different clinical presentations occur and why some patients are so resistant to therapy.\textsuperscript{38–40} For example, cutaneous inflammation that is histologically identical to SLE can occur in ANA-negative individuals. Moreover, in SLE patients, cutaneous inflammation can worsen while other organs are responding well to B cell depletion.\textsuperscript{41}

Downstream of antibodies and immune complexes, other genetic factors can have dramatic consequences on disease progression. One example is mutations of the \textit{APOL1} gene, which encodes apolipoprotein L1. Mutated alleles of \textit{APOL1} protect carriers against trypanosomiasis, which is the apparent reason for these mutations being common in some parts of Africa, but, if homozygous, make kidneys highly vulnerable to damage.\textsuperscript{42,43} This is particularly true for lupus nephritis, where immune complex disease leads to interferon production, which in turn induces \textit{APOL1} upregulation.\textsuperscript{44} This is at least one important explanation for why African Ancestry SLE patients are much more likely to suffer renal insufficiency after developing lupus nephritis.

With an unbiased approach, polyomics studies increase our understanding of the mechanisms of SLE and provide new information on the heterogeneity of the disease. We hope that these data will grow significantly in the next 10 years and help us (1) better understand the development of disease and specific disease features, (2) at least partially predict responses to therapy, and (3) identify SLE patients at particular risk for severe organ involvement and organ damage.

**Potential advance in diagnosis and assessment**

The structures of both the EULAR/ACR criteria\textsuperscript{14,15} and the earlier Systemic Lupus International Collaborating Centers (SLICC) classification criteria\textsuperscript{23} emphasized the importance of autoantibodies. Unfortunately, however, methodological problems and variability of several of the most relevant autoantibody tests have become apparent, such as issues with ANA testing, even on HEp-2 and HEp-2000 cells.\textsuperscript{45} Efforts to better standardize autoantibody testing are emerging. True progress regarding relevant new SLE autoantibodies has been limited. The discovery of antibodies against the dense fine speckled 70 kDa antigen (DFS70) was arguably the most relevant addition for physicians managing SLE patients – and those with suspected SLE. The presence of anti-DFS70 antibodies decreases the likelihood of SLE in any ANA-positive patient who does not have additional specific SLE antibodies.\textsuperscript{46,47} This is reassuring for individuals with usually relatively high titer ANA, which often were the result of testing because of nonspecific symptoms. While the major SLE autoantibodies will likely remain relevant in the future, we anticipate that further SLE autoantibody specificities are going to enter the arena. If so, we hope that this advance will not take another 10 years.

Immune complex deposition leads to the activation of complement pathways. Typically, complement C3 and C4 levels are measured, and reduced C3 or C4 is included in both the EULAR/ACR\textsuperscript{14,15} and the SLICC\textsuperscript{23} classification criteria. However, complement proteins are also acute phase reactants, which are overproduced in inflammatory conditions.\textsuperscript{48} Inflammation-driven overexpression of complement proteins may limit the sensitivity of the current tests, which essentially measure complement activation \textit{via} decreased levels. This problem can be overcome by analyzing complement split products, which are easier to detect on the membranes of blood cells. While the methods are clearly more complicated than those for just measuring C3 and C4, cell-bound complement split products are more sensitive for detecting complement activation.\textsuperscript{49} Cell-based complement split product assays will therefore likely be a welcome addition, provided that such tests will be sufficiently robust and broadly available in local laboratories.

Several cytokines and cytokine receptors, such as tumor necrosis factor (TNF) and soluble TNF receptor 2, correlate with SLE disease activity.\textsuperscript{50} While this association has been known for decades,\textsuperscript{51} it has never translated into routine clinical use, and we see no indication that it will in the near future. One exception, however, is type I interferons. These are best quantified by their
impact on immune cells, that is, the interferon signature.\textsuperscript{52,53} Although the differential effects of interferon receptor blockade with anifrolumab (see below) on patients with and without high interferon signature were less obvious in the phase III\textsuperscript{19} than in the phase II\textsuperscript{54} program, the type I interferon signature has the potential to become the first clinically actionable therapeutic biomarker in rheumatology. At the same time, there is a clear-cut association with disease activity.\textsuperscript{55} However, there is a diversity of approaches to quantification of type I interferon activity, and each of them has advantages and disadvantages. These include subsets of interferon-stimulated genes with stronger clinical associations, flow cytometric approaches, and single-molecule arrays.\textsuperscript{37,56–58} A EULAR Task Force has reviewed this literature and developed points-to-consider intended to progress these assays into clinical practice. Key elements of the research agenda are standardization of assay methodology and more appropriate clinical validation studies.

For lupus nephritis diagnosis, kidney biopsy remains the current standard\textsuperscript{17,59} and repeat biopsy is gaining importance.\textsuperscript{60} In addition, proteinuria has emerged as a robust predictor of long-term kidney outcome: based on Eurolupus data, and confirmed by GLADEL data, reducing proteinuria to not more than 0.7 g proteinuria by day or, more conveniently measured in spot urine, 0.7 g/g creatinine, is associated with excellent kidney outcomes.\textsuperscript{61–63} The ReBioLup study is assessing the value of repeat biopsies. We would therefore predict that, in 10 years from now, lupus nephritis will be assessed by a combination of proteinuria, repeat kidney biopsy, and novel urinary biomarkers.

Lupus arthritis is another area where methods of assessment are evolving. In the EULAR/ACR criteria project, palpable synovitis was tested against the more lenient SLICC definition,\textsuperscript{23} and outperformed by the latter.\textsuperscript{14,15} Lupus arthritis is not always palpable. The tools available for clearly differentiating between arthralgias and lupus arthritis that may still lead to Jaccoud-like arthropathy are magnetic resonance imaging and joint sonography,\textsuperscript{64–66} the latter being more practical for routine clinical use. In contrast to rheumatoid arthritis, where synovitis usually is clearly palpable, and where sonographic assessment has failed to show benefit over clinical assessment,\textsuperscript{67,68} sonography will likely play a more prominent role in the assessment of lupus arthritis.\textsuperscript{65,69,70} A recent trial has shown that ultrasound inflammation can identify patients who will benefit from therapy.\textsuperscript{69}

**A handful of novel drugs are expected**

An overall theme here is the promise of new classes of therapy. Historically, most conventional immunosuppressants and the most commonly used biologic therapies have targeted B cells. This may limit our ability to address the potential immune heterogeneity discussed above. But new therapies in development cover a far broader range of mechanisms of action. While this increases strategies available to physicians, it may also increase the need for stratification tools to make the best individual patient choices.

For some of the pipeline drugs, the outcome is already determined. The anti-interferon type I receptor antibody anifrolumab is already approved by the US Food and Drugs Administration (FDA) and the European Medicine Agency (EMA). Anifrolumab adds a different class of therapy to our armamentarium against nonrenal SLE. This may be particularly important when mucocutaneous manifestations, lupus arthritis, or hematological manifestations do not sufficiently respond to conventional therapy (Figure 2).\textsuperscript{19,54,71} In particular, previous work has suggested B cell-independent inflammation in cutaneous lupus, a disease manifestation with a strong association with the Type I IFN pathway and in which anifrolumab appears to be especially effective.\textsuperscript{41,72} Interferon receptor blockade appears to be more efficacious in patients with a high interferon signature, a feature that may help identify appropriate patients once these biomarkers are more widely available, although clinically and serologically active patients can usually be assumed to be IFN-signature positive.\textsuperscript{19} Data from a first phase II trial in lupus nephritis also suggest that anifrolumab may be efficacious in this critical inflammatory organ manifestation. Arguably, patients with the above-mentioned mutations in genes such as \textit{APOL1} might benefit from adding interferon receptor blockade early, since APOL1 is upregulated upon interferon influence.\textsuperscript{44} Indeed, a general principle that may emerge in stratification of targeted therapies may involve a greater understanding of differences between ancestral groups.

Based on positive phase II and III trials in lupus nephritis,\textsuperscript{21} the new calcineurin inhibitor voclosporin has been approved by the FDA for the treatment of lupus nephritis and will likely soon be
Voclosporin in combination with standard of care therapy with mycophenolate proved superior to standard of care alone. Therefore, voclosporin will be used as an add-on therapy. Voclosporin has possible advantages over existing calcineurin inhibitors, such as more predictable pharmacokinetics and pharmacodynamics, which obviate the need for therapeutic drug monitoring. Because calcineurin inhibitors have a direct impact on proteinuria via stabilization of the podocyte foot processes, we would envision voclosporin to become most useful in lupus nephritis patients with high levels of proteinuria, including those with membranous (class V) and with diffuse (class IV) nephritis developing nephrotic syndrome. Whether the drug will mostly remain in the initial phase of therapy or become a standard in lupus nephritis maintenance will depend on long-term data on nephrotoxicity, which is a concern with cyclosporin A and other older calcineurin inhibitors. Voclosporin will likely also be useful in nonrenal SLE manifestations, hematologic manifestations in particular. Even if there should not be controlled trials in nonrenal SLE, which would indeed be helpful, there will over time be information on the response of nonrenal SLE manifestations in lupus nephritis patients.

The next lupus nephritis drug likely to become relevant is obinutuzumab, a fully human, novel B-cell-depleting anti-CD20 antibody. In a phase II lupus nephritis trial, obinutuzumab was successful, when again added to standard of care therapy. Rituximab, the 20+ year standard in

| Manifestation          | Early         | Therapy Maintenance | Refractory     |
|------------------------|---------------|---------------------|----------------|
| Baseline (all SLE)     | Hydroxychloroquine Vitamin D | Hydroxychloroquine Vitamin D | Belimumab     |
| Lupus nephritis        | Cyclophosphamide Mycophenolate | Azathioprine Mycophenolate | Belimumab Tacrolimus |
|                        | Belimumab Voclosporin Obinutuzumab ? | Belimumab Voclosporin ? | Vocllosporin Obinutuzumab |
| Joint involvement      | Methotrexate Azathioprine Mycophenolate | Methotrexate Azathioprine Mycophenolate | Belimumab Leflunomide Etanercept |
| Mucocutaneous          | Methotrexate Azathioprine Mycophenolate | Methotrexate Azathioprine Mycophenolate | Anifrolumab Jak inhibitor CD40(L) blocker |
|                        |               |                     | Anifrolumab Jak inhibitor BIIB059 CD40(L) blocker |
| Hematologic            | Azathioprine Mycophenolate | Azathioprine Mycophenolate | Rituximab Cyclosporin |
|                        |               |                     | Anifrolumab CD40(L) blocker Obinutuzumab Vocllosporin Jak inhibitor ? |

Figure 2. Options of pharmacological SLE therapy now (light gray) and expected within 10 years (darker gray).
organ-threatening, refractory SLE, never managed to show such benefit in randomized controlled trials. While this may relate to problems in the design and conduct of older clinical trials in SLE, the efficacy of rituximab may also be limited by relatively inefficient B cell depletion in this disease, and obinutuzumab is designed for more complete tissue B cell removal. There is reasonable hope that the obinutuzumab phase III trial will be successful. If so, it will be important to understand where exactly B cell depletion will fit in the treatment paradigm. Apart from first-line use in induction therapy for lupus nephritis, based on the off-label experience with rituximab, we would surmise that this agent will have a role in refractory lupus nephritis as well as in other critical organ manifestations, such as central nervous system (CNS) or life-threatening hematological manifestations.

Among the cytokines definitely or likely relevant for SLE, at least the interferons and IL-6 depend on Janus kinase-1 (Jak1) in their signal transduction. Accordingly, Jak1 inhibitors, which in part also inhibit Jak2 and Jak3, have a good rationale for efficacy in SLE. While baricitinib showed efficacy in a phase II trial of nonrenal SLE, a recent press release announced the termination of the drug development program based on unconvincing phase III results. There are also trials with tofacitinib and upadacitinib, and rationale and phase II data combined may still suggest that Jak1 inhibitors may be a good option for lupus arthritis refractory to standard therapy. Blockade of the fourth Jak, Tyrosine kinase-2 (Tyk2), might be a more targeted therapeutic option. Tyk2 is necessary for type I interferon and IL-12 signaling. Because of the narrower focus, more complete blockade could be feasible, which would then potentially result in an oral drug with anifrolumab-like effects. The Tyk2 blocker deucravacitinib is currently being tested in SLE.

The inhibition of co-stimulation via CD28 and CD80/CD86 presumably will not continue to be studied in SLE in the wake of several negative trials of abatacept, mainly in lupus nephritis. In contrast, the T-cell–B-cell co-stimulatory pathway CD40 to CD40ligand (CD40L) does remain a hopeful SLE drug target. An earlier anti-CD40L antibody showed signs of efficacy, but led to platelet activation and thrombotic cardiovascular events. Two novel drug candidates block CD40–CD40L costimulation while avoiding platelet activation. Dapirolizumab-pegol is a pegylated F(ab)’ fragment of an anti-CD40L antibody, iscalimab instead blocks CD40. After positive signals with these drugs in phase II trials, phase III trials are underway. CD40 or CD40L blockade should lead to a profound reduction in autoantibody production and specific T cell functions, but may take time to modify inflammatory manifestations.

One additional candidate drug that has entered phase III trials is BIIB059, an antibody binding the BDCA2 receptor on plasmacytoid dendritic cells. These cells have been assumed to be prominent producers of interferon-α in SLE, although more recent data have indicated a less important role than previously thought. pDCs may also present antigen to T cells, although this function is also impaired in SLE pDCs. Hence, the mechanism of action of this therapy requires further study. Nevertheless, after success in a phase II trial, including significant effects on lupus arthritis and cutaneous LE, BIIB059 is currently undergoing phase III testing in SLE. Unless the other cytokines reduced should play a relevant role, it is still to be seen if BIIB059 is more effective than anifrolumab. After all, anifrolumab also blocks interferon-κ made by keratinocytes.

### Today’s drugs should remain relevant

The immunomodulatory SLE medications of today can be subdivided into three groups. To begin with, there are drugs that have a long onset of action, but are very safe in the long term and prevent SLE flares. This pertains to the antimalarials, and to belimumab. In contrast, there are the glucocorticoids, which work almost immediately, but often only in dose ranges that cause severe adverse effects in the longer term. And finally, there is a larger group of drugs that lead to anything from significant immunosuppression to immunomodulation, starting with cyclophosphamide and (higher dose) mycophenolate, rituximab, cyclosporin A, tacrolimus, and azathioprine. Many of these drugs are either not formally approved for SLE (methotrexate, mycophenolate, rituximab) or approved for some organ manifestations and in some regions only (e.g. cyclosporin A for class V nephritis, cyclophosphamide for lupus nephritis in Europe).

We believe that most of these drugs will continue to have some role in the treatment of SLE in the future.
decade to come. The two most likely exceptions are rituximab, which may be replaced by obinutuzumab, provided that this will be approved and not too expensive, and cyclosporin A, which plays a minor role as of today and may be replaced by voclosporin. Mycophenolate will probably be used more than azathioprine. However, mycophenolate is teratogenic and azathioprine is safe in pregnancy, and so there will still be need for azathioprine. Based on the same issue, low-dose cyclophosphamide, by Eurolupus regimen, will likely also remain an option, particularly for patients with lupus nephritis but hoping to limit ovarian toxicity to allow future pregnancy, and will remain a rescue medication. Methotrexate has its role in lupus arthritis, skin rashes, serositis, and mild vasculitis and is largely safe in nonpregnant patients with normal kidney function. We therefore think that methotrexate is also here to stay.

Virtually no one is going to bet against hydroxychloroquine (HCQ), which in Europe has remained an inexpensive drug. When keeping the dose range of up to 5 mg/kg actual body weight and performing adequate regular ophthalmological safety examinations, including visual field testing and optical coherence tomography, hydroxychloroquine is a very safe drug with considerable long-term efficacy and benefits for cardiovascular risk as well. Today’s standard will likely remain the standard for hydroxychloroquine in 10 years, even though novel toll-like receptor (TLR) antagonists may prove to be at least as effective and free of any retinopathy risks. Somewhat similarly, belimumab has gained an established position in keeping the disease controlled in patients who did not sufficiently respond to more basic measures, in reducing fatigue in a subset, and in doing so without relevantly increasing infections.

For glucocorticoids, there is not an alternative in sight that would be similarly versatile and available worldwide. While it is clear today that longer term doses should be kept low, to 5 mg prednisolone equivalent or lower, and while a subset of patients can be managed without glucocorticoids, both pulse glucocorticoids and short-term medium range prednisolone will remain important tools for rapidly reducing inflammatory disease activity. In the longer term, and for specific situations, complement inhibitors may obviate the need for higher dose glucocorticoids.

Medication adherence limits the effectiveness of current treatment strategies. The evolution of new therapies that include fewer pills with less common side effects and less complexity may increase the likelihood that patients with SLE can successfully treat their disease. Current SLE regimens frequently include at least three immunomodulatory medications (a glucocorticoid, HCQ, and an immunosuppressant), accompanied by supplementary medications to decrease long-term consequences of chronic illness, which include vitamin D and antihypertensives, in addition to medications to address gastrointestinal and physical discomfort. We hope that the future of SLE treatment includes simplified regimens to enhance adherence and an improved life experience for patients.

Lessons from COVID-19 and the risk of viral infections

Most of the immune mechanisms involved in active SLE have evolutionary developed for the purpose of controlling viral infections. Accordingly, effective SLE medications often increase the risk for viral infection and reactivation. Recent data on this risk profile came in two flavors. One, herpes zoster reactivation is relatively common even in young SLE patients. An increased risk of herpes zoster is also observed in the setting of treatment with Jak inhibitors and with the interferon receptor antagonist, anifrolumab. This is a problem that can be mitigated by herpes zoster vaccination, which is possible with a currently available highly effective nonlive vaccination. Zoster vaccination will very likely gain importance, until the majority of SLE patients will have been vaccinated against Varicella zoster virus as small children. Even when the Zoster problem is resolved, however, the mechanism could pertain to other virus, as well.

The other side is the ongoing COVID-19 pandemic. While we know now that SLE patients can mount antibody responses to both the infection and the major vaccines, they still have a higher risk of severe disease and poor outcomes. This was particularly true in the setting of treatment with higher dose glucocorticoids and rituximab. Moreover, both of these drugs, as well as mycophenolate, also reduce the efficacy of modern vaccines against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2).

Increased risks for more severe viral disease will presumably also be conferred by many of the novel drugs, including the anti-CD20 antibody.
obinutuzumab, but possibly also the anti-interferon receptor antibody anifrolumab, Jak inhibitors, or CD40/CD40L blockers. Beyond vaccination in time, temporal inefficacy of vaccines against novel pathogens will remain a risk for the future.

Is there the possibility of curing lupus?
Recent experience with the COVID-19 pandemic demonstrated the fact that lifelong immunosuppression is inherently risky. Accordingly, curing lupus must remain a goal. SLE is indeed one example of an autoimmune disease that could apparently be cured by resetting the immune system. Presumably, this will depend on eliminating both plasmablasts and long-lived plasma cells, and maybe also memory B cells, in order to eliminate the production of pathogenic autoantibodies (Figure 3). The most convincing available data are those from SLE patients treated with autologous stem cell transplantation (ASCT), with a regimen including antithymocyte globulin, and from lupus-prone mice who were treated with the proteasome inhibitor bortezomib. While ASCT is unfortunately associated with significant short-term mortality in SLE, most patients reach a state of longer term remission off therapy. ASCT leads to a full humoral reset, which also necessitates repeating all relevant vaccinations. Somewhat similarly, lupus mice can be very effectively treated with proteasome inhibition. This was not similarly effective in human SLE, but possibly also because of dose-limiting adverse effects of the available drugs.

The most novel approach that in singular cases led to similar results is chimeric antigen-receptor (CAR) T cell therapy against the CD19 receptor on B cells. In a pilot study, like in ASCT, the first patients with severe, organ-threatening SLE appeared to rapidly achieve remission and a constant decline in autoantibodies. Although it is not yet clear if long-lived plasma cells would be impacted by this therapy, the clinical data would be compatible with that possibility. Among the drugs tested without immediate success, there is at least one more candidate for immune reset: atacicept, TACI-IgG, was not sufficiently safe in

Figure 3. Curative options for antibody-mediated manifestations of SLE need to eliminate both plasmablasts and long-lived plasma cells.
its first SLE trial, because it also led to a fall in overall – and thus protective – immunoglobulin levels. By binding both BLyS/BAFF and APRIL, atacicept affects this whole cytokine and receptor system and would be expected to also impact plasma cells. Instead of trying to find a dose that is still effective while not unsafe, it might be more promising to try higher doses in order to bring about the necessary immune reset. The persistence of nonhematopoietic sources of type I IFN described above may be a mechanism of disease memory that is not targeted by most immunosuppressants. However, one must also note that ANA-positive individuals all have epidermal IFN-kappa production and most of them do not ever develop organ inflammation. The ‘second hit’ needed to move from stromal interferons to systemic autoimmune disease and inflammation is thus far unknown.

Another line of investigation offering the chance for drug-free remission is the concept of prevention. It is now recognized that ANA-positivity is a complex and dynamic immune state and that biomarkers may allow for the identification of patients destined to develop SLE and drug targets to prevent this. While we are somewhat doubtful that SLE cure will be a realistic routine scenario in 10 years, we hope to continue to make progress in that important direction.

**Figure 4.** Preventive options for SLE pregnancies now and expected in 10 years.

| Pregnancy issue            | Today                          | Possibly added by 2032          |
|----------------------------|--------------------------------|---------------------------------|
| Lupus activity             | Hydroxychloroquine             | Belimumab*                      |
|                            | Prednisolone                   | Anifrolumab*                    |
|                            | Azathioprine                   | CD40(L) blocker*                |
|                            | Cyclosporin A                  | Obinutuzumab*                   |
|                            | Tacrolimus                     | Voclorsporin§                   |
| Anti-phospholipid syndrome | Low dose aspirin (+LMW) heparines | Certolizumab-pegol              |
|                            | Hydroxychloroquine             |                                 |
| Preeclampsia               | Control of SLE activity        | Certolizumab-pegol              |
|                            | Low dose aspirin               | Higher dosing of aspirin        |
| Congenital heart block     | Hydroxychloroquine             | Maternal self-monitoring        |

**Toward safer lupus pregnancies**

SLE is a disease that disproportionately affects women of childbearing age. Fortunately, many women with SLE are able to have successful pregnancies. Treatment of antiphospholipid syndrome with heparins and low-dose aspirin has dramatically reduced adverse pregnancy outcomes, including pregnancy loss and thrombotic events. When SLE is well controlled prior to pregnancy, flares and adverse consequences on the fetus are less common. This is also true for lupus nephritis and other severe organ manifestations. Pregnancy outcomes have improved with the use of medications such as hydroxychloroquine, prednisolone, azathioprine, and calcineurin inhibitors (Figure 4). These medications can be safely used during pregnancy.

Determining more effective regimens to manage active SLE during pregnancy, potentially including some of the newer medications approved to treat SLE, is essential to improving outcomes for women and their offspring. In the meantime, ensuring all women with SLE receive accurate guidance about pregnancy prevention and pregnancy management is needed to increase the frequency that women with SLE are able to have healthy, term babies. The guidelines for management by ACR, British Society of Rheumatology, and EULAR all provide...
thorough background information for the medical care of pregnant and breast-feeding SLE patients. Putting these guidelines into practice, however, remains a challenge today.

Two significant problems remain. One is preeclampsia. This condition is life-threatening for both mother and fetus and often leads to premature delivery with many downstream negative consequences on fetal development. The routine use of aspirin has recently been an important step forward toward preeclampsia prophylaxis. Based on recent meta-analyses of pregnancies in women without rheumatic disease, the optimal dosing of aspirin may increase in coming years, particularly among women at very high risk or with aspirin resistance. At the same time, screening tools have improved, particularly in using the soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PLGF) ratio. For pregnant women with a high risk of preeclampsia despite aspirin and control of SLE disease activity, TNF blockade with certolizumab-pegol may improve pregnancy outcomes. Because of lack of missing the Fc portion of the antibody, certolizumab-pegol does not cross into the fetal circulation, which contributes to its improved safety profile.

Another important etiology of pregnancy morbidity is congenital heart block in the fetus of a mother with high titer anti-Ro-52 or anti-Ro-60 (and anti-La) antibodies. The risk of congenital heart block is low (around 2%), but the risk increases at least tenfold in mothers who have one child with congenital heart block. Progress in the last decade came with the observation that hydroxychloroquine reduces this rate by at least 50%. It is important that women with anti-Ro/La antibodies are appropriately screened for the occurrence of neonatal heart block, especially second-degree heart block, which is reversible. Over the next decade, screening for early heart block will likely evolve away from repeated fetal echocardiograms to twice-daily in-home evaluation using small, inexpensive power-Doppler devices.

with cutaneous manifestations. Current management strategies include a far greater variety of nonimmunomodulatory measures, which play a major role in reducing mortality and improving health-related quality of life. Such measures include control of hypertension and other vascular risk factors in all patients with SLE and particularly in patients with lupus nephritis, where RAAS blockade is essential. They also include all recommended standard vaccinations, including vaccinations against influenza, pneumococcus, human papilloma virus, herpes zoster, and now SARS-CoV-2. Recommendations also emphasize bone protection, with adequate vitamin D supplementation, and with antiresorptive agents when needed.

However, nonpharmacological approaches need to be better recognized and implemented. In SLE, there is a well-documented mismatch between physician-assessed disease activity and patient appraisal of their situation. Fatigue and pain are of high priority to patients, and both are only partly reversible by controlling disease activity. Secondary fibromyalgia is common in SLE. In order to facilitate the communication between SLE patients and their care providers, the concept of type 2 SLE symptoms has been developed. These symptoms, primarily fatigue and myalgias, may not be directly influenced by immunomodulatory therapies, but still need to be addressed. These are the symptoms, however, that patients most associate with SLE activity. In addition to multimodal pain management, where needed, and measures to restore quality of sleep, regular physical activity has a strong positive influence on fatigue and general well-being, and a proportion of SLE patients also need psychological and psychiatric support. With more focus on and better understanding of the interconnections between SLE disease activity, damage and psychological, social, and functional response patterns of the individual patients, these aspects are likely to be more successfully tackled in the next 10 years.

Progress in management beyond immunological interventions

Despite the central importance of immunomodulatory approaches in controlling this autoimmune disease, all major recommendations and guidelines on the management of SLE patients go beyond immunomodulation. For example, avoidance of UV exposure is not dispensable in patients

Thoughts on the worldwide perspective

Differences in genetic background, environmental factors, such as infectious risks, sun exposure and climate, or the circumstances of daily living, and in access to physicians experienced in caring for patients with SLE and to therapies, modify the characteristics and consequences of SLE. In addition, there are historical and
cultural differences in who takes responsibility in various situations and what is the local standard of therapy. Regarding the latter, more prominent use of tacrolimus in East Asia\textsuperscript{102,168–170} and the original restriction of reduced dose cyclophosphamide (Eurolupus regimen) to Europe\textsuperscript{4,171} are prominent examples. On the other hand, both of these therapies have been gaining global acceptance: tacrolimus entered the EULAR/ERA-EDTA guidelines\textsuperscript{17} and Eurolupus cyclophosphamide was shown to be effective also in African American patients.\textsuperscript{90} That the EULAR/ACR criteria were evaluated in the (Latin) American GLADEL and LUMINA cohorts\textsuperscript{172,173} as well as in China,\textsuperscript{174,175} Korea\textsuperscript{176} and Japan\textsuperscript{177} also manifests the willingness to arrive at common, data-driven standards for the care of SLE patients around the world.

While we are confident that the global SLE expert community will remain strongly committed to working together to improve the evidence base for SLE management, limited access to modern diagnostic and therapeutic means\textsuperscript{178–181} is more difficult to overcome. It remains a challenge that access to effective treatments is severely limited in some regions of the world, and novel medications are not available in even more places.\textsuperscript{182}

Conclusion
The momentum that has steadily increased in the SLE field over the past two decades has led to major advances in understanding and managing SLE in a data-driven way. These efforts will continue to lead to significant and steady progress. We are hopeful that both large polyomics studies and hypothesis-driven research will help to increase our understanding of SLE pathophysiology. Several new medications will augment our current therapeutic armamentarium, while most of today’s lupus drugs will remain relevant. In combination, these medications will lead to more commonly reaching remission or low disease activity, and enable the avoidance of doses of glucocorticoids that are damaging in the longer term. In addition, lupus pregnancies will become even safer, and growing understanding of type 2 SLE symptoms and appropriate non-pharmacological interventions will increase quality of life. Notably, global access to relevant SLE medications and discovery of a cure for SLE will remain challenging, yet critically important goals.

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