SLE is not a one-size-fits-all disease

In this Viewpoint we discuss how experimental medicine applied in the setting of clinical trials can address unmet need in the prototypic autoimmune disease systemic lupus erythematosus (SLE) to improve outcomes for patients.

Introduction

The benefits of dissecting the mechanisms of action of targeted therapies for autoimmune disease have been highlighted by several groups including our own some 15 yr ago (Ehrenstein and Mauri, 2007). We revisit this concept prompted by the continuing unmet need for patients with systemic lupus erythematosus (SLE).

To set the scene, we have included comparison with another autoimmune disease, rheumatoid arthritis (RA), where remission is now frequently attainable and a panoply of advanced therapies are widely available to support successful treat-to-target approaches (Fraenkel et al., 2021). Because of these novel treatments, guidelines for the management of RA have moved towards a position where corticosteroid use is not routinely recommended (Fraenkel et al., 2020), whereas patients with SLE often rely on corticosteroids with all their associated risks. Immunosuppressive agents, such as azathioprine, mycophenolate, and methotrexate, are frequently used off-label for patients with SLE, in part to minimize the use of corticosteroids. However, some lupus patients have disease that is refractory to these conventional therapies with increased risk of higher morbidity and mortality (Gordon et al., 2017). Of great concern is that there has been little improvement in lupus outcomes over recent decades in contrast to RA; SLE was amongst the leading causes of death in young women between 2000 and 2015 in the United States (Yen and Singh, 2018).

Considerable strides in the understanding of lupus pathogenesis have formed the bedrock of translational science for this disease and spearheaded the development and testing of novel treatments (van Vollenhoven, 2020). However, even the few therapies hailed as successful have required clinical trials that recruited many hundreds of participants (not an easy task with this uncommon, bordering on rare, disease) to demonstrate only modest efficacy compared to placebo. Trial design in lupus continues to evolve to overcome challenges that have been extensively discussed over the last 20 yr. The fact that the same agent can meet a primary endpoint in one trial but not another (Furie et al., 2019; Morand et al., 2020) and trials involving therapies broadly targeting the same pathway that report success and failure are a testament to these challenges. The delta in efficacy comparing the active and placebo arms range between 10 and 20% even in those positive trials, and coupled with high drug costs lead to restricted or no access to novel advanced therapies for patients with SLE in many countries. This is in contrast to rheumatoid arthritis, where the delta between active treatment and placebo is closer to 30–40%, therapies targeting the same pathway yield consistent results and active comparator (head-to-head) trials are frequently performed.

Disease heterogeneity in lupus exceeds that of most other diseases, including RA, and likely contributes to the variable outcomes in clinical trials. Ancestry is a vital component of disease heterogeneity and potentially variable response to treatment (Owen et al., 2022), and those with the worst disease can also be subject to social deprivation that can complicate the poor outcomes and barriers, which prevent access to these therapies (Carter et al., 2016). Ethnic minorities are underrepresented in lupus clinical trials but form the majority of lupus-prevalent cases and have the most active disease and worst outcomes (Falasinnu et al., 2018). Strategies to recruit more racial minorities into lupus clinical trials are needed, but could further increase the diversity in clinical outcome and therefore also increase the numbers of participants required to demonstrate a significant effect.

The issue of some patients, including from high-income countries, being denied or having restricted access to novel therapies is rarely discussed in the literature of SLE treatments or indeed in the academic meetings supporting advances in rheumatology. For example, anifrolumab, a type I interferon receptor antagonist now licensed for SLE, has had its appraisal for patients with SLE in England terminated in 2022 (and remains so at the time of writing) by NICE (https://www.nice.org.uk/guidance/ind/development/gid-ta10676). Cost per QALY thresholds imposed by NICE for these novel therapies may have been a factor in the decision by the manufacturers of anifrolumab to withdraw their submission. In contrast, at least one example of each advanced therapeutic class has been approved by NICE for patients with RA.

Identification of immune pathways that discriminate clinical response to targeted treatments would facilitate the introduction

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VIEWPOINT

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of clinical biomarkers to stratify patients with SLE according to response to specific agents. The consequent improvement in response rate would translate to more effective and therefore more affordable therapeutic strategies. The ease of the assay that measures a biomarker would aid its adoption in clinical practice and improve access to therapies for those patients most likely to respond. A comprehensive experimental medicine approach integrated within clinical trials for SLE would enable identification of these biomarkers. It is pertinent to note that although outcomes for RA have improved in recent times, the ambition of precision medicine for RA has yet to be realized and targeted therapies continue to be used on an empiric basis. But in general, a one-size-fits-all approach has been successful for advanced therapies for RA with broad access for patients in England to every class of treatment. This is not the case for SLE.

Rituximab for SLE: The most controversial drug in the history of lupus

It is with this background that the most controversial drug in the history of lupus has emerged: rituximab, which is used to deplete B cells. Although countless open-labeled studies and their metaanalyses indicated that rituximab was effective, it failed to demonstrate efficacy in two randomized controlled trials for SLE (Li et al., 2022). Notwithstanding these mixed results, rituximab remains the most widely used targeted therapy for SLE in England (McCarthy et al., 2017), though its availability and use around the world varies. In one study, SLE was the commonest diagnosis for off-label use of rituximab (Sarsour et al., 2020). For a time, rituximab was the only targeted therapy option for SLE, though restricted to patients with refractory disease, until belimumab became the first licensed treatment for lupus after a gap of 50 yr (Gordon et al., 2017). Even for years after licensing, belimumab had a prolonged route to acceptance and limited access for patients with SLE in England. Rituximab is now off patent, and acquisition costs can be cheaper than mycophenolate over a 6-mo period of therapy. No wonder then it has become the “love child” of lupologists: seldom recommended for the management of SLE at meetings but welcomed with open arms when prescribing for patients with refractory disease.

Rituximab’s mechanism of action has been extensively studied in patients with SLE partly to improve upon its effectiveness. Serum BAFF levels increase after rituximab, potentially driving B cell repopulation, and this rise is associated with lupus flares (Carter et al., 2013). This finding contributed to the development of the BEAT-lupus trial and several other trials testing the combination of the BAFF-targeting mAb belimumab after rituximab. Belimumab after rituximab significantly reduced the risk of severe lupus flares compared to placebo, both given after rituximab (Shipa et al., 2021). However, post-hoc analysis revealed that belimumab treatment increased the rate of a major clinical response at 52 wk compared to placebo, when both were given after rituximab, by 13%, which was not statistically significant (Shipa et al., 2022).

Experimental medicine applied to clinical trials can dissect lupus heterogeneity, reveal mechanisms of action, and generate theragnostic biomarkers

A plethora of outstanding studies using molecular phenotyping have stratified lupus patients into several groups, which could account for the heterogeneous response to targeted therapies (Banchereau et al., 2016; Figgert et al., 2019; Nakano et al., 2022; Panousis et al., 2019). There was limited correlation between organ involvement and molecular endotypes across these studies. It has been hoped that stratification of patients will aid treatment selection and improve outcomes, given the immunopathological and clinical complexity of SLE combined with variable and overall modest response to therapy. However, as with genetic association studies, the impact of molecular stratification has yet to be realized with respect to new treatments for SLE. Despite the limited efficacy of new therapies and variation in response among patients, the field has not yet advanced to the point where participants in clinical trials are stratified according to molecular phenotyping. Indeed, classification of lupus according to molecular signatures has rarely been performed in the setting of a clinical trial testing a targeted therapy against placebo. Immunosuppressant treatments have a significant impact on gene expression modules in SLE (Northcott et al., 2022). Therefore, longitudinal analysis of a well-defined clinical cohort in a placebo-controlled trial can reduce the variation compared to cross-sectional or longitudinal studies where treatment is not placebo controlled and allows for more precise analysis of changes in immune signatures over time with respect to a specific therapy. This has been achieved using samples from a clinical trial of tabalumab, which like belimumab targets BAFF (Toro-Dominguez et al., 2022). The response prediction probabilities were significantly different in patients treated with tabalumab compared to placebo and were principally derived from gene modules related to B cells and plasma cells. Efforts to reduce the confounding effects of immunosuppressants on clinical response and molecular phenotypes in the context of clinical trials are also required, and cessation of these medications, as well as tapering corticosteroids, will help to identify effective therapies.

Recognizing the potential value of the BEAT-lupus trial for reverse translational research, blood samples were collected from participants. Following a machine-learning approach applied to the analysis of these trial samples, baseline serum IgA2 anti-dsDNA antibody levels emerged as the strongest predictor of response to belimumab after rituximab, and a lack of response to rituximab alone (Shipa et al., 2022). The response rate to the combination increased from 48% in unselected patients to 64% in those patients with high serum IgA2 anti-dsDNA antibody levels at baseline, and revealed a 48% difference compared to placebo (Shipa et al., 2022). Similarly, the reduction in the risk of a severe flare (BILAG-2004 grade A) with belimumab compared to placebo was more marked in participants with a high serum IgA2 anti-dsDNA antibody level at baseline. Moreover, belimumab after rituximab, compared to rituximab and placebo, significantly reduced serum IgA2 anti-dsDNA levels and circulating IgA2 secreting plasmablasts from baseline to 52 wk only in patients who responded to therapy. Of relevance, the formation of neutrophil extracellular traps (NETs) was reduced by the combination of belimumab after rituximab in the Synbiose trial (Kraaij et al., 2018), consistent with observations that IgA2 is more effective in inducing NET formation than IgA1 and indeed IgG complexes (Gimpel et al., 2022; Steffen et al., 2020).
The biomarker analysis of BEAT-lupus reveals the potential for a targeted therapy to tease apart its mechanisms of action to reveal the immune pathogenesis of a lupus endotype specifically responsive to belimumab after rituximab. It was fortuitous that a simple ELISA identified the key biomarker, thus providing a relatively easy route to adoption in routine clinical practice to guide treatment with rituximab followed by belimumab combination therapy. The analysis of serum IgA2 anti-dsDNA antibody levels as a theragnostic biomarker in patients receiving belimumab alone, as well as other trials testing the combination of rituximab and belimumab, would be a critical prelude to a clinical trial where patients could be stratified according to serum IgA2 anti-dsDNA antibody levels as a theragnostic biomarker to targeted therapies in SLE which can be used to stratify patients. Conventional approaches to understanding disease pathogenesis and heterogeneity in SLE focus on cross-sectional and longitudinal studies. But with randomized clinical trials testing targeted therapies, the effects of treatment are more rigorously controlled not only through comparative longitudinal analysis of the active versus placebo arm from baseline and several timepoints thereafter but also with the increasing practice of tapering concomitant immune suppressive therapies. Profiling patients within a clinical trial can deconvolute disease heterogeneity in SLE and reveal a disease endotype that responds to the targeted therapy under evaluation. The identification of a biomarker for that endotype enables stratification in a subsequent clinical trial. Eventually this approach applied to several different treatments could potentially provide therapeutic strategies for a spectrum of distinct lupus endotypes.
dsDNA antibody levels. The anticipated substantial increase in difference between the active treatment and placebo when patients are stratified according to serum IgA2 anti-dsDNA antibody levels should result in fewer patients required to meet the pre-specified endpoint.

Conclusions
A one-size-fits-all approach has been successful for developing targeted therapies in rheumatoid arthritis but less so for patients with SLE. Molecular stratification of patients in lupus clinical trials should become an essential component of the experimental medicine journey of specific rheumatic diseases (Fig. 1). If results from the BEAT-lupus trial are confirmed, gatekeepers such as NICE could be persuaded to increase access to advanced therapies for a selected group of patients with SLE most likely to respond, thereby adopting a precision medicine approach where the cost per QALY is reduced to more acceptable levels. Indeed, this experimental medicine strategy could also rescue therapies that may be effective for a sub-group of patients but that have been dropped by the company because of a failure to demonstrate an overall benefit. The eventual goal will be to move closer to guidelines for SLE where remission can be attained without corticosteroids for subgroups of patients particularly responsive to specific targeted therapies, rather than allowing the gap in outcomes between SLE and RA to increase further.

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References