Systemic lupus erythematosus: one year in review 2024

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ABSTRACT

Systemic lupus erythematosus (SLE) is classically regarded as the landmark of systemic autoimmune diseases, characterised by protean, multi-systemic manifestations and a highly variable clinical course.

Over the last years, both clinical and translational clinical research efforts led to significant steps forward in management and treatment of SLE. However, numerous aspects of SLE, from pathogenesis to treatment, still remain challenging, and several unmet needs persist for both patients and physicians. Following the previous annual reviews of this series, herewith, we aim to report the most relevant new updates on SLE, issued in 2023. In particular, we focused on biomarkers, clinical aspects and outcomes, comorbidities, as well as new treatment targets and real-world evidence.

Introduction

SLE is a chronic autoimmune condition with a complex and not yet fully clarified pathogenesis that results in heterogeneous clinical and serological disease manifestations. According to the setting of the *One year in review* series (1), we aim to provide a brief critical digest of the latest findings about SLE.

We performed a MEDLINE search of English language articles published from 1st January to 31st December 2023 using MESH terms and free text words for the following search keys: systemic lupus erythematosus AND biomarkers, clinical manifestations, patient-reported outcomes, comorbidities, phase III and post-marketing studies, registries, real-world evidence, preclinical and phase I-II clinical studies. We reviewed all the articles and selected the most relevant papers, excluding reviews and case-reports.

Biomarkers

During 2023, further efforts to identify novel biomarkers have been made, reflecting the increasing need for more precise and non-invasive disease indicators that may help in clinical practice. Indeed, new biomarkers could represent a turning point of several unmet needs in SLE, from earlier diagnosis to disease flare prediction, up to clinical phenotypes assessment, disease activity monitoring and specific organ involvement detection, in order to achieve better disease management and treatment.

One of the most important topics in this field concerns type I interferon (IFN) signalling pathway, serum IFN activity, interferon-induced genes, and proteins.

A retrospective longitudinal observational study showed for the first time that serum IFN activity at baseline correlated with disease activity in treatment-naive SLE patients; in particular, in these patients IFN activity was significantly associated with fever, haematologic disorders, and mucocutaneous manifestations and it decreased along with a decrease in disease activity after therapy. Thus, serum IFN activity at baseline may be a potential useful biomarker to evaluate disease status in SLE patients (2).

In a cohort of 90 patients hospitalised for acute severe lupus and high disease activity, serum IFN-α levels resulted a better predictor of in-hospital mortality than global disease activity markers like Systemic Lupus Disease Activity Index (SLEDAI), or serological markers (dsDNA and C3). These findings suggested that serum IFN-α may serve also as a valuable prognostic biomarker of severe disease, allowing for more aggressive disease management and treatment strategies (3).

By whole-genome sequencing of mRNA in peripheral blood mononuclear cells from SLE patients and

healthy controls, Wang *et al*. found that over-expressed levels of IFI44L (interferon-induced protein 44 like genes) in SLE patients could be a promising biomarker of the disease, with a high potential usefulness in clinical diagnosis, serving as a potential reference index for the diagnosis of SLE due to its high sensitivity and specificity (4).

Serum samples from 422 SLE patients, 546 healthy controls (HCs), and 1.223 patients with other autoimmune diseases (AIDs) were analysed for a selection of autoimmunity-related cytokines and autoantibodies within the frame of the European PRECISESADS project. Several IFN-inducible proteins (BAFF, CCL8, CXCL10, and CXCL11) were elevated in SLE patients compared with HCs. Serum levels of CCL8, CXCL13, and IL-1RA were higher in patients with active, but not inactive, SLE *versus* HCs, as well as in patients with SLE *versus* other AIDs. Levels CCL8, CXCL13, and IL-1RA were moderately correlated with global SLE disease activity suggesting that they could be a useful serum biomarker of activity in SLE (5).

Lupus nephritis (LN) is a severe complication of SLE and in the last year, several studies focused on biomarkers of lupus nephritis. A study that analysed 104 kidney biopsies from LN patients, showed that higher renal IFI16 (Interferon-inducible protein 16) expression was associated with an increase in disease activity and worse prognosis, meaning that it could be an effective biomarker, particularly to predict the renal response to the treatment (6).

Using a quantitative protein microarray, Tang *et al*. screened for high-abundant proteome expression in the serum of patients with LN compared to healthy controls. VSIG4 (V-set immunoglobulin domain-containing protein 4) upregulation resulted the most promising marker in distinguishing LN from healthy controls, allowing also a good discrimination between active and inactive LN; indeed, it positively correlated with several clinical and pathologic parameters of LN, especially the renal pathology activity index scores potentially reflecting the extent of disease activity (7).

Results from a prospective case-control study on a cohort of adult patients with SLE, suggested that soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is significantly associated with SLE activity; in particular, urinary sTREM-1 levels resulted correlated positively with renal-SLEDAI score, inversely with serum C3 and C4 levels, and positively with proteinuria suggesting that it may serve as a biomarker for active LN (8).

Differentiation of immature NK cells (Im NK) into mature NK cells (MD NK) reflects the ability of NK cells to respond to cytokines whereas dedifferentiation between NK cell subpopulations may suggest loss of immune homeostasis in SLE. Li *et al*. compared, by a flow cytometry analysis, peripheral blood NK cell sub-populations between SLE patients and HCs and among patients with different levels of disease activity; they observed an increased Im NK-to-MD NK ratio in SLE, which correlated with disease activity parameters and LN, suggesting that the imbalance in Im NK/MD NK may be a potential biomarker of disease activity and renal involvement (9).

The lack of objective markers of neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) have encouraged studies aimed at discovering novel biomarkers in cerebrospinal fluid (CSF) that could increase diagnostic accuracy for NPSLE.

With this aim, Ni *et al*. used a quantitative planar protein antibody microarray to screen 1000 proteins in CSF from SLE patients without NPSLE, NPSLE patients and healthy controls. The study identified five differently expressed proteins with distinct expression patterns: KLK5, L-selectin, Trappin-2, TCN2, and CST6 which exhibited the best accuracy in discriminating NPSLE patients. Thus, these biomarkers were applied to build potential diagnostic models for NPSLE and to distinguish NPSLE patients from SLE patients and controls (10).

In the same field, a study by Fujita *et al*. aimed to investigate potential biomarkers of diffuse NPSLE. The authors found that Montgomery-Asberg Depression Rating Scale (MADRS)-positive SLE patients with depressive symptoms have decreased levels of neuroinflammatory markers such as HVA (homovanillic acid) SDF-1a (cell-derived factor-1a) and SCGF-1b (stem cell growth factor-b) in CSF (11).

In the B cells development, a part of autoreactive B cells is suppressed via induction of anergy by peripheral tolerance. Anergic autoreactive B cells (BND cells) reactivation seems to be a key process in SLE pathogenesis.

A study by Liu *et al*. showed that IL-4 is a type 2 cytokine that can reverse B cell anergy by increasing surface-IgM (sIgM) through the interruption of sIgM internalisation, and by promoting sIgM stability, via STAT6 signalling. Thus, blocking IL4-mediated signalling could represent a novel potential therapeutic strategy in SLE (12).

Take home messages

- Type I IFN signalling pathway, serum IFN activity, interferon-induced genes or proteins correlate with disease activity, predict in-hospital mortality, and could be used as a potential index for SLE diagnosis (2), (6).
- VSIG4 is a promising marker to evaluate renal disease activity, differentiating active from inactive LN or LN from HCs (7).
- KLK5, L-selectin, Trappin-2, TCN2, and CST6 in cerebrospinal fluid could help to identify neuro-psychiatric involvement in SLE (10).

Clinical aspects and outcomes

The significant challenge posed by the heterogeneity of SLE is widely recognised. The lack of specific symptoms and the broad spectrum of potential organ involvement frequently led to diagnostic delay. In an observational study mapping lupus patients' journey, the median delay from symptom onset to diagnosis was 24 months. Only 28.4% of patients received an early diagnosis, while 55.6% were diagnosed after 12 months and consulted three physicians before diagnosis (13).

Interestingly, in a large cohort of patients with recent onset SLE, younger disease onset seems to correlate with a more active immunological profile, while late onset with a higher incidence of comorbidities (14).

Another common characteristic of SLE is the frequent occurrence of disease flares, influencing patient outcomes and survival. Cuhna *et al*. identified predictors of flares in SLE patients in lupus low disease activity state (LLDAS) (15). Over three years, 28.4%, 24.7%, and 13.4% experienced flares. Predictors of SLE-DAS (SLE disease activity score) flares included anti-U1-ribonucleoprotein presence (hazard ratio (HR) = 2.16, 95% CI 1.30–3.59), baseline SLE-DAS score (HR=1.27, 95% CI 1.04–1.54), and immunosuppressant use (HR=2.43, 95% CI 1.43–4.09) (15). A further longitudinal study characterised difficult-to-treat extra-renal flares using a machine learning approach, revealing that among clinical data not being in a state of LLDAS after 3 months was the unique independent predictor of difficult-to-treat flares. Specifically, mild-to-moderate flares with mucocutaneous manifestations in patients with a history of skin involvement were associated with the lowest remission rates (16). Finally, in a cohort of active SLE patients, renal involvement, haematological involvement, and hypocomplementaemia were identified as negative predictors for achieving and maintaining LLDAS (17). Notably, achieving LLDAS at 3 months emerged as a positive predictor for the long-term sustainment of LLDAS (17).

Once again, over the past year, there has been significant attention on major complications of SLE, particularly focusing on the involvement of the renal and central nervous systems. In the context of lupus nephritis, a Danish study utilising data from the DANBIO registry evaluated the probability of new-onset proteinuria among SLE patients at 1, 5, and 10 years (18). The analysis identified two factors associated with the development of new-onset proteinuria: lymphopenia, with a HR of 1.77 (95% confidence limits, 95CI 1.24–2.52), and discoid rash, with an HR of 0.42 (95CI 0.21–0.83). Male patients with lymphopenia showed the highest predicted risks of developing proteinuria, ranging from 9% to 89% over 1, 5, and 10 years, depending on the age of onset (20, 30, 40, or 50 years) (18).

The assessment of 24-hour proteinuria levels is crucial in the management of lupus nephritis, and the reduction in 24-hour proteinuria levels is part of the endpoints used in clinical studies. In this context, evaluating the changes in trajectories of 24-hour proteinuria over time in patients with lupus nephritis under standard-of-care (SoC) in a real-world setting is of particular relevance. In a renal biopsy-proven lupus nephritis cohort, four trajectories of urine protein changes over time were identified using a semi-supervised machine learning approach: rapid responders, good responders, suboptimal responders, and non-responders. For 'rapid responders,' the nomogram included age, disease duration, albumin, and 24-hour proteinuria, yielding C-indices >0.85. The nomogram to predict 'good responders' comprised gender, new-onset LN, glomerulosclerosis, and partial remission within 6 months (19).

The end-stage renal disease (ESRD) represents a relevant complication of lupus nephritis. A retrospective study assessed the risk of ESRD in patients with early-onset lupus nephritis compared to delayed-onset LN (20). Examining data from 3779 incident SLE patients, with 60% having early-onset lupus nephritis and 40% having delayed-onset LN, the study found that the overall risk of ESRD was comparable between the two groups. However, in patients undergoing aggressive immunosuppressive therapy, delayed-onset LN was associated with a higher risk of ESRD compared to early-onset lupus nephritis (20). These results emphasise the importance of considering the timing of LN onset and treatment strategies in managing the risk of ESRD.

The importance of achieving deep remission in LN patients has been clearly demonstrated by Kikuchi *et al*. (21); in a longitudinal cohort of patients receiving induction therapy for active LN, they found that patients with deep remission within 12 months experienced a significantly lower rate of subsequent renal flare and damage accrual than those without complete renal response and those with remission after 12 months.

The neuropsychiatric involvement in SLE is consistently considered one of the most intricate and challenging aspects of the disease. Indeed, recent observations highlighted the fact that patients with major central nervous system (CNS) involvement experienced a higher annual mortality rate (10.8%) compared to those without (3.8%) (22). In the study by Magro-Checa *et al*., major CNS involvement, particularly cerebrovascular disease, and organic brain syndrome, independently emerged as prognostic factors for poor survival (22). Evaluating cognitive function is crucial, given that this manifestation adversely affects health-related quality of life and leads to limitations in daily activities.

A multicentre study aimed to phenotype SLE based on symptom burden, with a special focus on cognitive function Using Similarity Network Fusion (SNF). Two distinct subtypes (A and B) emerged among 238 SLE patients (23). Subtype A exhibited poorer objective and subjective cognitive function, higher disease burden/damage, and lower health-related quality of life with respect to subtype B.

A further study highlighted relative stability in cognition over time for most individuals with SLE (24). Perera *et al*. investigated cognitive changes over 7 years in 1281 adults with SLE. The analysis, utilising the Hopkins Verbal Learning Test-Revised and Controlled Oral Word Association Test, revealed minimal transitions between cognitive states. Higher self-reported depression correlated with a decreased likelihood of cognitive improvement while increasing age and higher education levels were associated with cognitive improvement. Additionally, greater self-reported SLE disease severity and depression were linked to cognitive decline (24). Increasing attention is being directed towards sleep disturbances in patients with SLE, viewed as potential manifestations of neuropsychiatric lupus. Preliminary data from a survey involving over 1800 SLE and other autoimmune rheumatic disease patients aimed at exploring the frequency, impact, timing, and response to treatment of various neuropsychiatric symptoms, including nightmares, and indicated a higher prevalence of these issues in SLE patients compared to a healthy co-

hort. The authors suggested that nightmares and disrupted sleep patterns in SLE may indicate heightened cerebral arousal linked to immunological inflammation (25). In a further cross-sectional study, SLE patients exhibited poorer sleep maintenance, increased total sleep time, and higher perceived stress compared to age- and gender-matched healthy controls (26). Daily glucocorticoid dose in SLE patients was linked to impaired sleep maintenance, while perceived stress was associated with short sleep duration (26). In conclusion, these findings underscore the intricate nature of sleep disturbances in SLE, emphasising the necessity for a comprehensive and multidimensional approach to fully understand their clinical significance.

Take home messages

- Anti-U1-ribonucleoprotein presence, baseline SLE-DAS score, and immunosuppressant use are identified as predictors of flares in patients on lupus low disease activity state (LLDAS) (15). Difficult-to-treat extrarenal flares are associated with not achieving LLDAS after 3 months (16).
- In patients with lupus nephritis, delayed-onset lupus nephritis is associated with a higher risk of ESRD, particularly in patients undergoing aggressive immunosuppressive treatment (20).
- Neuropsychiatric involvement in SLE is intricate and impactful, with major CNS issues linked to a higher annual mortality rate (22).
- Sleep disturbances, including nightmares, indicate heightened cerebral arousal, emphasising the need for a comprehensive approach to understanding and managing these manifestations in SLE (25), (26).

Comorbidities and organ damage

Patients with SLE share high comorbidities burden, and the recently released EULAR recommendations for the management of the disease state that comorbidities (along with other factors, such as organ manifestations and risk for progressive damage) should direct individualised pharmacological treatment approaches (27).

However, a standardised approach for evaluation of the comorbidities burden has not been purposed so far. To this regard, in a population-based registry analysis (Minnesota and Wisconsin), the authors assessed the prevalence of multimorbidity, defined as the coexistence of two or more chronic conditions apart from SLE (28). In the "established SLE" cohort (449 patients with established diagnosis *vs*. 450 non-SLE), 366 patients had multimorbidity (82%), mostly non-SLICC/ACR Damage Index (SDI)-related, with an odds ratio (OR) three-fold higher than non-SLE (OR 2.98, 95%CI 2.18–4.11). In the "incident" cohort (270 new-onset SLE and 280 controls), 154 (57%) already had multimorbidity (OR 2.27, 1.59–3.27) and, in the other half, the risk of acquiring multimorbidity along the disease course was almost twice than non-SLE comparators.

Exploring a different concept borrowed from geriatric medicine, Lima *et al*. assessed the frailty in a prevalent cohort of 149 women with established SLE (29). Frailty is a proxy for biological age which captures the clinical heterogeneity of individuals with similar risks and outcomes, depicting the capacity of individuals to respond to stress factors. In this work, each 0.05-unit increase in the baseline SLICC Frailty Index (SLICC-FI) score was associated with higher risk of subsequent damage accrual (OR 1.28, 1.01–1.63), while the baseline SDI values were not, thus suggesting that frailty can introduce a further complexity in the evaluation of SLE patients susceptible to damage.

Moreover, in clinical practice, the co-occurrence of different autoimmune diseases is common. A large UK population-based study (22,009,375 individuals), based on primary and secondary electronic health records from the Clinical Practice Research Datalink (CPRD), demonstrated that SLE, along with Sjögren's syndrome and systemic sclerosis, had the higher co-occurrence rate of other autoimmune diseases, regardless of diagnostic sequence and after accounting for age and sex (30). Apart from reflecting a common pathogenic process, this evidence should be considered in the individualisation of treatment paradigms, particularly with the availability of novel biologics.

Although several immunosuppressants have been found to increase the risk of infections in SLE, a consisting augmented risk is related to the disease-itself, and this is particularly true for young adults. In a large administrative database analysis from the U.S. with over 1,700,000 hospital admission in SLE patients (2010–2019), the serious infection-related hospitalisations in young adults (18–24 years) were similar to that of adults (25–44 years) with SLE, but significantly higher compared to non-SLE young adults (15% *vs*. 4%), particularly for sepsis and pneumonia. This contributes significantly to the morbidity of this age-group population, especially in Black, Hispanic and Asian (with respect to White) ethnicities (31).

Additional knowledge in this field was provided by the study of Larsen *et al*. (32), reporting on the humoral immune response and risk of disease flare in SLE patients following three-doses of SARS-CoV-2 vaccines. The study demonstrated that the 3rd dose improved the humoral response to SARS-CoV-2 vaccines to the level of healthy individuals without affecting disease activity; moreover, subsequent breakthrough infections were mild and did not require hospitalisation, suggesting the good effectiveness of the vaccination.

Besides the infectious risk, SLE patients notably manifest significantly higher cardiovascular (CV) risk with reference to non-SLE population: however, which is the correct screening tool to be adopted in SLE patients for CV risk estimation remains not clear. A recent study examined whether generic and disease-adapted CV risk scores are able to predict subclinical atherosclerosis progression in SLE (33). Among 124 patients without clinically established coronary artery disease, SLE-adapted risk scores, such as QRISK3 and mFRS, performed better than the generic tools in predicting the development of new atherosclerotic plaques (3 years of follow-up), thus suggesting that SLE-adapted CV risk scores might better contribute to the interception of subclinical atherosclerosis disease development.

Together with comorbidities, the concept of damage should be contextualised in the perspective of a correct resource use. In a UK cohort study (n=936), the accrual of damage within 5 years in newly-diagnosed SLE patients was significantly associated with increased annualised per-patient costs, with higher primary (care and prescriptions) and secondary (hospital admission and emergency) healthcare resource use (34). Opposingly, it should be noted that damage accrual, particularly glucocorticoid-related (OR 1.22, 95%CI 1.09–1.38), was associated with the number of attending physicians in a multicentre cohort study from Japan (35), thus claiming for a careful thinking of the structure of the Lupus Clinics in developing phases. However, it must be underlined that the concept of "SLE-related damage" is not static in its nature. The SLICC, the Lupus Foundation of America (LFA), and the ACR have started a collaborative effort to develop a revised damage index. Through a cross-sectional qualitative study, Johnson *et al*. hypothesised that a new concept of damage should be a measure of morbidity in SLE, independent of disease activity and patients' impact, but related to mortality (36). Rheumatologists should start thinking that damage might occur even before a diagnosis of SLE and that, despite irreversible, the functional consequences on one organ may improve over time. This more flexible concept of damage carries the possibility to impact on future SLE research.

Take home messages

- The modality of assessment of the comorbidities burden in SLE has not been yet standardised, but the concepts of multimorbidity and frailty should be considered (28), (29).
- SLE-adapted cardiovascular risk scores might be able to predict better than generic tools the subclinical atherosclerosis disease development (33).
- The construction of the concept of "SLE-related damage" is changing and aims at measuring in a more flexible way the SLE-related morbidity, impacting on future SLE research (36).

New treatment targets

In the last year, new insights into the pathogenesis of SLE provided novel potential treatment targets as molecules and technologies studied both in animal models and through phase 1 trials.

Pre-clinical and phase I studies

Toll-like receptor (TLR) 7 and TLR8 are endosomal sensors of the innate immune system; their chronic activation is linked to the pathogenesis of SLE. (37)

E6742, a dual TLR7 and TLR8 antagonist, was used in two mouse models of SLE (NZB/W and pristane-induced) by Ishizaka *et al*. who demonstrated that oral E6742 administered after the onset of disease suppressed the increase in autoantibodies (anti-ribosomal P protein) and blocked the advance of organ damage (arthritis scores and proteinuria) (38).

Based on these promising results of the pre-clinical phase (38), Yamakawa *et al*. conducted the First-in-Human phase I trial on E6742: good safety and tolerability was demonstrated in 42 healthy volunteers; interestingly, cytokine concentrations in cultured peripheral blood in response to E6742 were suppressed in a dose-dependent manner (39).

Spleen tyrosine kinase (Syk) plays a pivotal role in the activation of B cells and innate inflammatory cells. Dysregulated activity of Syk has been implicated in the development of SLE. Cho *et al*. showed that a novel selective Syk inhibitor, Cevidoplenib, ameliorates lupus nephritis in murine models, decreasing the levels of IgG autoantibody, proteinuria, and glomerulonephritis (40).

Another promising agent against SLE is Rozibafusp alfa (AMG 570), a first-in-class bispecific IgG2-peptide fusion, designed to inhibit inducible T-cell costimulatory ligand (ICOSL) and B-cell activating factor (BAFF). Altered interactions between ICOS/ICOSL and BAFF have been implicated in SLE pathogenesis by driving autoantibody and cytokine production (41). Preclinical studies demonstrated greater efficacy with dual blockade than blockade of either pathway alone (42). Rozibafusp alfa clinical pharmacokinetic was characterised in a phase I trial on 65 healthy subjects: it exhibited nonlinear pharmacokinetic and dose-related, reversible, dual-target engagement. Naive B cell counts were reduced, indicating dose-and exposure-dependent BAFF inhibition. A dose and concentration-dependent increase in ICOSL occupancy reflected rozibafusp alfa/target engagement (43).

Phase 2 and 3 clinical trials

Non-receptor tyrosine-protein kinase 2 (TYK2) is one of the most promising targets in the treatment of SLE. This intracellular kinase mediates signalling of key cytokines involved in the pathogenesis of the disease, including type I interferons (IFNs), interleukin-10 (IL-10), IL-12 and IL-23.

Deucravacitinib is an oral, selective, allosteric inhibitor of TYK2, approved by FDA for the treatment of adults with moderate-to-severe plaque psoriasis (44).

The phase II trial (PAISLEY) was designed to evaluate the efficacy and safety of deucravacitinib in adult patients with active SLE. The primary endpoint was SLE Responder Index 4 (SRI-4) response at week 32. The percentage of patients achieving SRI-4 response was 34% with placebo compared to 58% with deucravacitinib 3 mg twice daily, 50% with 6 mg twice daily and 45% with 12 mg once daily. Rates of adverse events were similar across groups, except higher rates of infections and cutaneous events, including rash and acne, with deucravacitinib treatment (45). These results support the potential benefits of TYK2 inhibition in SLE to be explored in larger phase III trials.

Inhibiting both BLyS and APRIL is another promising approach for treating SLE, with the potential to provide more complete inhibition of autoantibody production (46).

Telitacicept is a novel fusion protein that binds to the extra-cellular BLyS/APRIL-binding portion. Telitacicept showed promising efficacy (37) and an acceptable safety profile in patients with active SLE in a phase 2b clinical trial (47). At week 48, the proportion of patients achieving an SRI-4 response was 75.8% in the 240 mg telitacicept group,

68.3% in the 160 mg group, 71.0% in the 80 mg group and 33.9% in the placebo group (all $p<0.001$). Telitacicept was well tolerated, and the incidence of adverse events and serious adverse events were similar between the telitacicept and placebo groups.

On the other hand, some promising molecules in earlier studies failed to demonstrate efficacy in phase II trials; among these Evobrutinib, a highly selective, orally administered, Bruton's tyrosine kinase (BKT) inhibitor. BTK plays an important role in B cell signalling, thus it could be involved in the pathogenesis of SLE. However, the phase II trial (NCT02975336) dose-ranging trial in SLE failed to show a treatment effect of evobrutinib *versus* placebo at any dose (48).

Similarly, Baricitinib, a Janus kinase inhibitor, has been another potential candidate for the treatment of SLE: during the last year two phase III studies (SLE-BRAVE I (49) and SLE-BRAVE II (50)) were published, evaluating efficacy and safety of baricitinib 4 mg compared to SoC in active non-renal SLE.

However, the primary endpoint (proportion of patients achieving an SLE Responder Index (SRI)-4 response at week 52 in the baricitinib 4 mg treatment group versus placebo) was only achieved in SLE-BRAVE I, while both confirm the known safety profile. Moreover, an integrated safety analysis of baricitinib in patients with SLE found no increased risk of venous thromboembolism (51).

Belimumab

In 2023 new pivotal data have been published also on Belimumab, the recombinant, human IgG1λ monoclonal antibody that binds to the soluble B-lymphocyte stimulator protein, already approved for the treatment of non-renal SLE.

The phase 3 study BLISS-LN was the largest controlled study in active LN to date, which demonstrated that the addition of intravenous (IV) belimumab to standard therapy improves renal outcomes in patients with LN (52).

Thereafter, several *post-hoc* analyses on Belimumab trials were published in the last year.

Among these, as data on treatment of East Asian patients with LN are limited, Yu *et al*., evaluated the efficacy and safety of belimumab in the BLISS-LN East Asian subgroup; this subset's analysis results were consistent with those of the overall BLISS-LN population and support the benefits of belimumab treatment across kidney outcomes in SLE (53).

Interestingly, Hans-Joachim *et al*. performed a *post-hoc* analyses of the phase 3 BLISS-LN study to assess belimumab efficacy on kidney-related outcomes in newly diagnosed and relapsed LN subgroups showing that Belimumab improved kidney outcomes compared with placebo regardless of whether patients had newly diagnosed or relapsed LN (54).

Gomez *et al*. pooled data from the BLISS-52, BLISS-76, BLISS-SC, and BLISS-Northeast Asia trials of belimumab (3225 patients) to determine the effect of antimalarial agents (AMA) and different doses and routes of administration of belimumab on preventing renal flares in patients with SLE treated for extra-renal disease. Compared with placebo, the risk of renal flares was lower among patients receiving intravenous belimumab 10 mg/kg or intravenous belimumab 1 mg/kg. The protection against renal flares conferred from belimumab was increased in the presence of antimalarials (55).

Since phase III trials of belimumab excluded patients with severe CNS involvement, little is known about the potential benefits of this drug in the treatment of neuropsychiatric SLE (NPSLE).

Palazzo *et al*. aimed to determine the ability of belimumab to protect against NPSLE events, analysing data from five phase III trials: the addition of belimumab to SoC did not offer any clear protection from the occurrence of NPSLE flare (56).

Anifrolumab

Anifrolumab is a human monoclonal antibody that targets type I IFN receptor subunit 1 recently approved for the treatment of SLE. In the last year several *post-hoc* analyses from TULIP trials have been published, providing important information on the efficacy and safety of the drug.

In a *post-hoc* analysis of the phase III studies TULIP-I and TULIP-II, Bruce *et al*. found both a sustained reduction of glucocorticoids (GCs) in patients treated with anifrolumab (51%) compared to placebo (32%) concomitant to an overall disease activity reduction (38% in anifrolumab-treated patients *vs*. 23% in placebo-treated patients) (57).

From the same trials, Morand *et al*. demonstrated that patients treated with anifrolumab had an earlier, more frequent, and more prolonged achievement of LLDAS compared to placebo (58).

Moreover, Bruce *et al*., evaluating the time course of clinical response following anifrolumab treatment showed that anifrolumab arm experienced an early improvement in overall SLE disease activity and skin responses compared to placebo from week 8 onwards and possibly leading to a greater reduction in GCs starting from week 20 (59).

A 3-year extension study of the TULIPI-1 and TULIP-2 trials was published by Kalunian *et al*., showing the long-term safety and tolerability of anifrolumab in active SLE with no new safety findings (60).

Tanaka *et al*. in a sub analysis of TULIP-II trial reported the same efficacy and safety profile of the drug in the Japanese patients' subgroup (61).

As far as lupus nephritis is concerned, Jayne *et al*. published the results of the second-year extension study of the phase II trial (TULIP-LN) of anifrolumab in lupus nephritis, confirming the efficacy of the drug in improving disease renal outcomes with an acceptable safety profile of the drug (62).

Voclosporin

Voclosporin is a calcineurin inhibitor that has been recently approved in combination with Mycophenolate Mofetil for the treatment of LN. In the last year, interesting new data have been published on this drug.

Among these, Arriens *et al*. have performed an integrated analysis across different racial and ethnic groups, confirming the efficacy and safety of voclosporin in the treatment of LN (63).

Take home messages

- Deucravacitinib (inhibitor of TYK2), elicited higher response rates compared with placebo, with an acceptable safety profile, in adult patients with active SLE (45).
- Telitacicept shows promising efficacy and an acceptable safety profile in patients with active SLE in a phase 2b trial (47).
- Patients treated with anifrolumab had an earlier, more frequent, and more prolonged achievement of lupus low Disease Activity State (LLDAS) compared to placebo (58).
- Voclosporin in the treatment of LN demonstrated efficacy and safety across different racial and ethnic groups (63).

Treatment: real-world evidence

In the last decade, real-life evidence in rheumatology is becoming increasingly significant, due to the relatively recent release of new treatments and the urgency of discovering their potential and effective applications in clinical practice.

Belimumab

Most of SLE real-world evidence available in 2023 focused on belimumab, providing new data on safety and effectiveness of this drug from real-clinical settings.

In a multicentre study (64) of 188 active SLE patients, most of them with a difficult-to-treat, longstanding disease, belimumab was effective in reducing disease activity and steroid use, and in facilitating the achievement of therapeutic targets. Moreover, trying to identify patient subsets who were more likely to benefit from belimumab, trajectories analysis of activity indices was performed: consistent with previous reports, baseline physician global assessment (PGA), prior mycophenolate use, leukopenia, and cutaneous inflammatory rash were found to be predictors of clinical response.

A recent mono-centric work (65) evaluated belimumab effectiveness in Japanese SLE patients with moderate-to-high disease activity. Treatment with belimumab significantly reduced the mean SLEDAI-2K and prednisone-daily dose from baseline. Additionally, belimumab, mycophenolate, mycophenolate plus belimumab and intravenous cyclophosphamide treatment groups have been compared. No significant differences among groups in the flare-free survival rates or in the SLEDAI-2K scores decline were found, although several limitations due to small sample size, retrospective observational design, and confounders, affected study results.

In line with previous reports, new real-world evidence for belimumab's steroid-sparing effect came from the Patient-Important Outcomes Data Repository (PIONEER) database (66). This large US rheumatology network provided data about oral steroid use in more than a thousand patients who started belimumab treatment, showing significant lowering in daily steroid dose with greater reductions observed with increasing duration of belimumab administration.

A large multicentre observational study (67) produced robust real-life data about Chinese lupus patients on belimumab. 244 subjects were enrolled and stratified according to SELENA-SLEDAI score in mild or moderate-to-severe disease activity subgroups. They received intravenous belimumab as add-on therapy and were matched and compared to control arm patients on SoC alone in a mean follow-up period of 1 year. In this Chinese population, belimumab showed efficacy in reducing disease activity, improving serologic markers, facilitating glucocorticoid tapering, and, therefore, achieving LLDAS/remission treatment-targets at 12 months, in line with real-life observational studies on other populations. Among patients with mild disease activity, after propensity score matching there was a 2-fold decrease of flare events with significantly lower risk of disease flare and major flare in belimumab add-on patients with respect to the control group.

Evidence of belimumab effectiveness in refractory lupus nephritis was provided in a recent, multicentre study (68). Forty-five Chinese patients who failed induction therapy with SoC were enrolled and received 24 weeks belimumab infusion as add-on therapy. Despite a short follow-up period, belimumab treatment showed a significant steroid dose-sparing effect and facilitated achievement of complete (13% of patients) and partial (42%) renal response, maintaining a good safety profile in this peculiar and fragile subset of patients. Therefore, these data from real-clinical settings suggest a possible role of belimumab as add-on therapy in refractory lupus nephritis in patients of Asian ancestry.

About belimumab exposure during pregnancy, a descriptive summary of data from clinical trials, belimumab pregnancy registry (69), and post-marketing/spontaneous reports has been published (70). Available records about birth defects and miscarriages in belimumab-exposed pregnancies were reported. Unfortunately, several limitations, due to low sample size, confounders, heterogeneous and missing data, prevented comparisons and conclusions on drug-associated risks for adverse pregnancy outcomes. As a result, current available evidence still precludes informed recommendations regarding belimumab use during pregnancy.

Anifrolumab

First safety and efficacy real-world data of anifrolumab treatment in SLE came from Japanese LOOP registry (71): 45 patients, receiving anifrolumab for 12 to 26 weeks, were compared with SoC controls. Patients in anifrolumab therapy were classified, based on LLDAS, in 3 different groups: those who were not on LLDAS despite standard-of-care, those who achieved LLDAS with the SoC but experienced minor flares, and others who were on LLDAS with SoC therapy with the target of remission or GCs dose reduction. Anifrolumab showed effectiveness in all subgroups, allowing improvement of disease activity and GCs dose reduction. Particularly, in line with TULIP-1 and TULIP-2 clinical trial results, anifrolumab significantly lowered the required GC dose among those patients who achieved LLDAS but subsequently experienced minor disease flares mainly due to articular or mucocutaneous manifestations. It is noteworthy that the primary endpoint of the study was a high retention rate, which was approximately 90% at 26 weeks after initiating anifrolumab therapy.

Take-home messages

- 2023 real-life data confirmed effectiveness of belimumab in steroid dose-sparing, facilitating the achievement of treatment targets with a good safety profile (64-67).
- Robust evidence on belimumab exposure during pregnancy is still lacking, precluding new informed recommendations issue for patients of childbearing age (69-70).
- First real-life data on anifrolumab therapy are available, showing a high retention rate, significant improvement in disease activity and GC dose reduction, particularly in patients experiencing minor flares after LLDAS achievement (71).

Conclusions

We hereby selected some of the most significant research works on SLE released during 2023. In this review we aimed to cite and summarise the novel insights from the past year, covering several aspects of this complex disease, with particular focus, in line with the *One Year in Review* collection, on their potential implications in clinical practice.

References

1. ZUCCHI D, SILVAGNI E, ELEFANTE E *et al*.: Systemic lupus erythematosus: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(5): 997-1008. https://doi.org/10.55563/clinexprheumatol/4uc7e8
2. MIYACHI K, IWAMOTO T, KOJIMA S *et al*.: Relationship of systemic type I interferon activity with clinical phenotypes, disease activity, and damage accrual in systemic lupus erythematosus in treatment-naive patients: a retrospective longitudinal analysis. *Arthritis Res The*r 2023; 25(1): 26. https://doi.org/10.1186/s13075-023-03010-0
3. YERRAM KV, BAISYA R, KUMAR P, MYLAVARAPU R, RAJASEKHAR L: Serum interferon-alpha predicts in-hospital mortality in patients hospitalised with acute severe lupus. *Lupus Sci Med* 2023; 10(2): e000933. https://doi.org/10.1136/lupus-2023-000933
4. WANG Y, JA W, MA Q *et al*.: Identification of IFI44L as a new candidate molecular marker for systemic lupus erythematosus. *Clin Exp Rheumatol* 2023; 41(1): 48-59. https://doi.org/10.55563/clinexprheumatol/q3aa6s.
5. LINDBLOM J, BERETTA L, BORGHI MO, ALARCÓN-RIQUELME M E, PARODIS I: Serum profiling identifies CCL8, CXCL13, and IL-1RA as markers of active disease in patients with systemic lupus erythematosus. *Front Immunol* 2023; 14: 1257085. https://doi.org/10.3389/fimmu.2023.1257085
6. WANG X, FU S, YU J *et al*.: Renal interferon-inducible protein 16 expression is associated with disease activity and prognosis in lupus nephritis. *Arthritis Res Ther* 2023; 25(1): 112. https://doi.org/10.1186/s13075-023-03094-8
7. TANG C, ZHANG S, TEYMUR A *et al*.: V-SET immunoglobulin domain-containing protein 4 as a novel serum biomarker of lupus nephritis and renal pathology activity. *Arthritis Rheumatol 2023*; 75(9):1573-85. https://doi.org/10.1002/art.42545
8. MOLAD Y, EGBARIA M, TOVAR A *et al*.: Urine soluble triggering receptor expressed on myeloid cells-1 is a novel biomarker for active lupus nephritis: a case-control study. *Clin Exp Rheumatol 2023*; 41(7):1451-55. https://doi.org/10.55563/clinexprheumatol/4lvaye.
9. LI H, GENG L, CAO Z *et al*.: CD56bright-CD16- to CD57+CD56dimCD16+ NK cell ratio discriminates disease activity and renal involvement in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2023; 41(9):1768-76. https://doi.org/10.55563/clinexprheumatol/o6bjl8.
10. NI J, CHEN C, WANG S *et al*.: Novel CSF biomarkers for diagnosis and integrated analysis of neuropsychiatric systemic lupus erythematosus: based on antibody profiling. *Arthritis Res Ther* 2023; 25(1):165. https://doi.org/10.1186/s13075-023-03146-z
11. FUJITA Y, IWATA S, HIDESE S *et al*.: Reduced homovanillic acid, SDF-1α and SCGF-β levels in cerebrospinal fluid are related to depressive states in systemic lupus erythematosus. *Rheumatology* (Oxford) 2023; 62(10): 3490-500. https://doi.org/10.1093/rheumatology/kead091
12. LIU Y, ZHANG Z, KANG Z *et al*.: Interleukin 4-driven reversal of self-reactive B cell anergy contributes to the pathogenesis of systemic lupus erythematosus. *Ann Rheum Dis* 2023; 82(11): 1444-54. https://doi.org/10.1136/ard-2023-224453
13. KAPSALA NN, NIKOLOPOULOS DS, FLOUDA SP *et al*.: From first symptoms to diagnosis of systemic lupus erythematosus: mapping the journey of patients in an observational study. *Clin Exp Rheumatol* 2023; 41(1): 74-81. https://doi.org/10.55563/clinexprheumatol/x3s9td
14. PREVETE I, IULIANO A, CAULI A *et al*.: Similarities and differences between younger and older disease onset patients with newly diagnosed systemic lupus erythematosus. Clin Exp Rheumatol 2023; 41(1): 145-50. https://doi.org/10.55563/clinexprheumatol/oo5ymg
15. CUNHA RN, SARAIVA L, JESUS D, DORIA A, DA SILVA JP, INÊS L: Predictors of flare in SLE patients fulfilling lupus low disease activity state: A cohort study of 292 patients with 36-month follow-up. *Rheumatology* (Oxford) 2023; 62(11): 3627-35. https://doi.org/10.1093/rheumatology/kead097
16. MAFFI M, TANI C, CASCARANO G *et al*.: Which extra-renal flare is 'difficult to treat' in systemic lupus erythematosus? A one-year longitudinal study comparing traditional and machine learning approaches. *Rheumatology* (Oxford) 2024; 63(2): 376-84. https://doi.org/10.1093/rheumatology/kead166
17. ZHANG K, AN Y, ZHAO P *et al*.: Predictors and prognostic stratification for lupus low disease activity state: results from a prospective clinical trial. *Rheumatology* (Oxford) 2023; 62(3): 1153-61. https://doi.org/10.1093/rheumatology/keac419
18. ANDERSEN M, STOCKMARR A, LEFFERS H CB *et al*.: Absolute risk estimation of new-onset proteinuria in patients with systemic lupus erythematosus: a Danish nationwide cohort study. *Clin Exp Rheumatol* 2023; 41(11): 2264-68. https://doi.org/10.55563/clinexprheumatol/rk2dxp
19. ZHANG D, SUN F, CHEN J *et al*.: Four trajectories of 24-hour urine protein levels in real-world lupus nephritis cohorts. *RMD Open* 2023; 9(2): e002930. https://doi.org/10.1136/rmdopen-2022-002930.
20. CHO S-K, KIM H, HAN J-Y *et al*.: Risk of end-stage renal disease in patients with early-onset lupus nephritis: A population-based cohort study. *Semin Arthritis Rheum* 2023; 63: 152308. https://doi.org/10.1016/j.semarthrit.2023.152308
21. KIKUCHI J, HANAOKA H, SAITO S *et al*.: Deep remission within 12 months prevents renal flare and damage accrual in lupus nephritis. *Clin Exp Rheumatol* 2023; 41(7): 1500-6. https://doi.org/10.55563/clinexprheumatol/7yv1dz
22. MAGRO-CHECA C, RAMIRO S, RÙA-FIGUEROA I *et al*.: Central nervous system involvement in systemic lupus erythematosus: Data from the Spanish Society of Rheumatology Lupus Register (RELESSER). *Semin Arthritis Rheum* 2023; 58: 152121. https://doi.org/10.1016/j.semarthrit.2022.152121
23. BARRACLOUGH M, ERDMAN L, DIAZ-MARTINEZ JP *et al*.: Systemic lupus erythematosus phenotypes formed from machine learning with a specific focus on cognitive impairment. *Rheumatology* (Oxford) 2023; 62(11): 3610-18. https://doi.org/10.1093/rheumatology/keac653
24. PERERA S, COOK R, LEE K-A, KATZ P, TOUMA Z: Intraindividual change in cognitive function among adults with systemic lupus erythematosus: a Markov analysis over 7 years. *ACR Open Rheumatol* 2023; 5(3): 124-31. https://doi.org/10.1002/acr2.11529
25. D'CRUZ DP, SLOAN M: Clinical observation: are nightmares a manifestation of neuropsychiatric lupus? *Rheumatology* (Oxford) 2023; 62(6): 2030-31. https://doi.org/10.1093/rheumatology/keac655
26. FARAGUNA U, PORCIANI C, COLITTA A *et al*.: Actigraphic and self-reported characterization of sleep in systemic lupus erythematosus patients. *Rheumatology* (Oxford) 2023 Jul 11. https://doi.org/10.1093/rheumatology/kead344
27. FANOURIAKIS A, KOSTOPOULO M, ANDERSEN J *et al*.: EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024; 83(1): 15-29. https://doi.org/10.1136/ard-2023-224762
28. FIGUEROA-PARRA G, MEADE-AGUILAR JA, HULSHIZER CA *et al*.: Multimorbidity in systemic lupus erythematosus in a population-based cohort: the Lupus Midwest Network. *Rheumatology* (Oxford) 2023 Nov 24. https://doi.org/10.1093/rheumatology/kead617
29. LIMA K, LEGGE A, HANLY JG *et al*.: Association of the systemic lupus international collaborating clinics frailty index and damage

accrual in longstanding systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2023; 75(3): 578-84. https://doi.org/10.1002/acr.24798
30. CONRAD N, MISRA S, VERBAKEL JY *et al*.: Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet* 2023; 401(10391): 1878-90. https://doi.org/10.1016/S0140-6736(23)00457-9
31. DHITAL R, GUMA M, POUDEL DR, CHAMBERS C, KALUNIAN K: Infection-related hospitalisation in young adults with systemic lupus erythematosus: data from the National Inpatient Sample. *Lupus Sci Med 2023*; 10(1): e000851. https://doi.org/10.1136/lupus-2022-000851
32. LARSEN ES, NILSSON AC, MÖLLER S, VOSS AB, JOHANSEN IS: Immunogenicity and risk of disease flare after a three-dose regimen with SARS-CoV-2 vaccination in patients with systemic lupus erythematosus: results from the prospective cohort study COVAC-SLE. *Clin Exp Rheumatol* 2023; 41(3): 676-84. https://doi.org/10.55563/clinexprheumatol/b8a6zb
33. PANOPOULOS S, DROSOS GC, KONSTANTONIS G, SFIKAKIS PP, TEKTONIDOU MG: Generic and disease-adapted cardiovascular risk scores as predictors of atherosclerosis progression in SLE. *Lupus Sci Med* 2023; 10(1): e000864. https://doi.org/10.1136/lupus-2022-000864
34. STIRNADEL-FARRANT HA, GOLAM SM, NAISBETT-GROET B *et al*.: Healthcare resource use and costs associated with organ damage in newly diagnosed adults with systemic lupus erythematosus in the UK. *Rheumatol Ther* 2023; 10(5): 1183-97. https://doi.org/10.1007/s40744-023-00567-9
35. YANAI R, YAJIMA N, OGURO N *et al*.: Number of attending physicians and accumulated organ damage in patients with systemic lupus erythematosus: LUNA registry cross-sectional study. *Rheumatol Ther* 2023; 10(2): 421-31. https://doi.org/10.1007/s40744-022-00528-8
36. JOHNSON SR, GLADMAN DD, BRUNNER HI *et al*.: Evaluating the construct of damage in systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2023; 75(5): 998-1006. https://doi.org/10.1002/acr.24849
37. ALPER P, BETSCHART C, ANDRE' C *et al*.: Discovery of the TLR7/8 antagonist MHV370 for treatment of systemic autoimmune diseases. *ACS Med Chem Lett* 2023; 14(8): 1054-62. https://doi.org/10.1021/acsmedchemlett.3c00136
38. ISHIZAKA S T, HAWKINS L, CHEN Q *et al*.: A novel Toll-like receptor 7/8-specific antagonist E6742 ameliorates clinically relevant disease parameters in murine models of lupus. *Eur J Pharmacol* 2023; 957: 175962. https://doi.org/10.1016/j.ejphar.2023.175962
39. YAMAKAWA N, TAGO F, NAKAI K *et al*.: First-in-human study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of E6742, a dual antagonist of toll-like receptors 7 and 8, in healthy volunteers. *Clin Pharmacol Drug Dev* 2023; 12(4): 363-75. https://doi.org/10.1002/cpdd.1176
40. CHO S, JANG E, YOON T, HWANG H, YOUN J: A novel selective spleen tyrosine kinase inhibitor SKI-O-703 (cevidoplenib) ameliorates lupus nephritis and serum-induced arthritis in murine models. *Clin Exp Immunol* 2023; 211(1): 31-45. https://doi.org/10.1093/cei/uxac096
41. SULLIVAN B A, TSUJI W, KIVITZ A *et al*.: Inducible T-cell co-stimulator ligand (ICOSL) blockade leads to selective inhibition of anti-KLH IgG responses in subjects with systemic lupus erythematosus. *Lupus Sci Med* 2016; 3(1): e000146. https://doi.org/10.1136/lupus-2016-000146
42. ZHANG M, LEE F, KNIZE A *et al*.: Development of an ICOSL and BAFF bispecific inhibitor AMG 570 for systemic lupus erythematosus treatment. *Clin Exp Rheumatol* 2019; 37(6): 906-14.
43. ABUQAYYAS L, CHEN P-W, DOS SANTOS MT *et al*.: Pharmacokinetics and pharmacokinetic/pharmacodynamic properties of Rozibafusp Alfa, a bispecific inhibitor of BAFF and ICOSL: analyses of phase I clinical trials. *Clin Pharmacol Ther* 2023; 114(2): 371-80. https://doi.org/10.1002/cpt.2929
44. TRUONG TM, PATHAK GN, SINGAL A, TARANTO V, RAO BK: Deucravacitinib: the first FDA-approved oral TYK2 inhibitor for moderate to severe plaque psoriasis. *Ann Pharmacother* 2024; 58(4): 416-27. https://doi.org/10.1177/10600280231153863
45. MORAND E, PIKE M, MERRILL JT *et al*.: Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2023; 75(2): 242-52. https://doi.org/10.1002/art.42391
46. SAMY E, WAX S, HUARD B, HESS H, SCHNEIDER P: Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. *Int Rev Immunol* 2017; 36(1): 3-19. https://doi.org/10.1080/08830185.2016.1276903
47. WU D, LI J, XU D *et al*.: Telitacicept in patients with active systemic lupus erythematosus: results of a phase 2b, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2024; 83(4): 475-87. https://doi.org/10.1136/ard-2023-224854
48. WALLACE DJ, DÖRNER T, PISETSKY DS *et al*.: Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib in systemic lupus erythematosus: results of a Phase II, randomized, double-blind, placebo-controlled dose-ranging trial. *ACR Open Rheumatol* 2023; 5(1): 38-48. https://doi.org/10.1002/acr2.11511
49. MORAND EF, SMOLEN JS, PETRI M *et al*.: Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I). *Lancet* 2023; 401(10381): 1011-19. https://doi.org/10.1016/S0140-6736(22)02546-6
50. PETRI M, BRUCE IN, DÖRNER T *et al*.: Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *RMD Open* 2023; 9(3): e003302. https://doi.org/10.1136/rmdopen-2023-003302
51. MORAND E, SMOLEN J S, PETRI M *et al*.: Safety profile of baricitinib in patients with systemic lupus erythematosus: an integrated analysis. *RMD Open* 2023; 9(3): e003302. https://doi.org/10.1136/rmdopen-2023-003302
52. FURIE R, ROVIN B H, HOUSSIAU F *et al*.: Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; 383(12): 1117-28. https://doi.org/10.1056/NEJMoa2001180
53. YU X, CHEN N, XUE J *et al*.: Efficacy and safety of belimumab in patients with lupus nephritis: subgroup analyses of a phase 3 randomized trial in the East Asian population. *Am J Kidney Dis* 2023; 81(3): 294-306.e1. https://doi.org/10.1053/j.ajkd.2022.06.013
54. ANDERS H-J, FURIE R, MALVAR A *et al*.: Effect of belimumab on kidney-related outcomes in patients with lupus nephritis: post hoc subgroup analyses of the phase 3 BLISS-LN trial. *Nephrol Dial Transplant* 2023; 38(12): 2733-42. https://doi.org/10.1093/ndt/gfad167
55. GOMEZ A, JÄGERBACK S, SJÖWALL C, PARODIS I: Belimumab and antimalarials combined against renal flares in patients treated for extra-renal systemic lupus erythematosus: results from 4 phase III clinical trials. *Rheumatology* (Oxford) 2024; 63(2): 338-48. https://doi.org/10.1093/rheumatology/kead25
56. PALAZZO L, LINDBLOM J, CETREZ N, ALA H, PARODIS I: Determinants of neuropsychiatric flares in patients with systemic lupus erythematosus: results from five phase III trials of belimumab. *Rheumatology* (Oxford) 2024; 63(3): 798-808. https://doi.org/10.1093/rheumatology/kead249
57. BRUCE I N, VAN VOLLENHOVEN RF, MORAND EF *et al*.: Sustained glucocorticoid tapering in the phase 3 trials of anifrolumab: a post hoc analysis of the TULIP-1 and TULIP-2 trials. *Rheumatology* (Oxford) 2023; 62(4): 1526-34. https://doi.org/10.1093/rheumatology/keac491
58. MORAND EF, ABREU G, FURIE RA, GOLDER V, TUMMALA R: Lupus low disease activity state attainment in the phase 3 TULIP trials of anifrolumab in active systemic lupus erythematosus. *Ann Rheum Dis* 2023; 82(5): 639-45. https://doi.org/10.1136/ard-2022-222748
59. BRUCE IN, VAN VOLLENHOVEN RF, PSACHOULIA K *et al*.: Time to onset of clinical response to anifrolumab in patients with SLE: pooled data from the phase III TULIP-1 and TULIP-2 trials. *Lupus Sci Med* 2023; 10(1): e000761. https://doi.org/10.1136/lupus-2022-000761
60. KALUNIAN KC, FURIE R, MORAND EF *et al*.: A randomized, placebo-controlled Phase III extension trial of the long-term safety and tolerability of anifrolumab in active systemic lupus erythematosus. *Arthritis Rheumatol* 2023; 75(2): 253-65. https://doi.org/10.1002/art.42392
61. TANAKA Y, ATSUMI T, OKADA M *et al*.: The efficacy and safety of anifrolumab in Japanese patients with systemic lupus erythematosus: TULIP-2 subanalysis. *Mod Rheumatol* 2023; 33(1): 134-44. https://doi.org/10.1093/mr/roac010
62. JAYNE D, ROVIN B, MYSLER E *et al*.: Anifrolumab in lupus nephritis: results from second-

year extension of a randomised phase II trial. *Lupus Sci Med* 2023; 10(2): e000910. https://doi.org/10.1136/lupus-2023-000910
63. ARRIENS C, TENG Y KO, GINZLER EM *et al*.: Update on the efficacy and safety profile of voclosporin: an integrated analysis of clinical trials in lupus nephritis. *Arthritis Care Res* (Hoboken) 2023; 75(7): 1399-408. https://doi.org/10.1002/acr.25007
64. NIKOLOUDAKI M, NIKOLOPOULOS D, KOUTSOVITI S *et al*.: Clinical response trajectories and drug persistence in systemic lupus erythematosus patients on belimumab treatment: A real-life, multicentre observational study. *Front Immunol* 2023; 13: 1074044. https://doi.org/10.3389/fimmu.2022.1074044
65. SUMICHIKA Y, YOSHIDA S, SUZUKI E *et al*.: Real-world effectiveness of belimumab in patients with active lupus. *J Clin Med* 2023; 12(24): 7627. https://doi.org/10.3390/jcm12247627
66. WORLEY K, MILLIGAN S, RUBIN B: Steroid-sparing effect of belimumab: results from a retrospective observational study of real-world data. *Lupus Sci Med* 2023; 10(2): e001024. https://doi.org/10.1136/lupus-2023-001024
67. SUN F, WU H, WANG Z *et al*.: Effectiveness and safety of belimumab in Chinese lupus patients: a multicenter, real-world observational study. *Biomedicines* 2023; 11(3): 962. https://doi.org/10.3390/biomedicines11030962
68. ZHANG S, QIU Q, ZHENG S *et al*.: Response to belimumab among patients with refractory lupus nephritis: a real-world observational retrospective multicenter study. *Clin Rheumatol* 2024; 43 (1): 199-208. https://doi.org/10.1007/s10067-023-06817-z
69. JULIAO P, WURST K, PIMENTA JM *et al*.: Belimumab use during pregnancy: Interim results of the belimumab pregnancy registry. *Birth Defects Res* 2023; 115(2): 188-204. https://doi.org/10.1002/bdr2.2091
70. PETRI M, LANDY H, CLOWSE MEB *et al*.: Belimumab use during pregnancy: a summary of birth defects and pregnancy loss from belimumab clinical trials, a pregnancy registry and postmarketing reports. *Ann Rheum Dis* 2023; 82(2): 217-25. https://doi.org/10.1136/ard-2022-222505
71. MIYAZAKI Y, FUNADA M, NAKAYAMADA S *et al*.: Safety and efficacy of anifrolumab therapy in systemic lupus erythematosus in real-world clinical practice: LOOPS registry. *Rheumatology* (Oxford) 2023 Nov 2. https://doi.org/10.1093/rheumatology/kead568