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Article *in* British Journal of Rheumatology · November 2020

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doi:10.1093/rheumatology/keaa672

Concise Report

European League Against Rheumatism (EULAR) recommendations and EULAR/American College of Rheumatology criteria—documenting progress in lupus

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Within 1 year the EULAR published four papers on aspects of SLE. First came the 2019 update of the EULAR recommendations for the management of SLE [1], then the EULAR recommendations for the management of APS in adults [2] and, as the latest addition, the 2019 update of the joint EULAR and European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) recommendations for the management of LN [3]. In between, the EULAR/ACR 2019 classification criteria for SLE were published [4].

These publications each represent the work of a rather large group of experts, which often took several years to complete. Taken together, the papers have 112 individual authors, and the groups involved were in fact considerably larger. Accordingly, one would hope that the results mirror the efforts. Indeed, we believe that the four papers are important milestones towards better management of SLE patients all over Europe and beyond. In some ways these publications, all derived from both evidence and expert consensus, document progress made rather than coming up with great surprises.

The lack of real news was occasionally bemoaned, and it is a fact that a number of positive trial results were announced after the respective EULAR publications went public. These recent successes include the first positive phase III trial on anifrolumab, the antibody against the common type I interferon receptor [5], and the positive LN trials with belimumab, the novel anti-CD20 antibody obinutuzumab, and voclosporin, which were not yet published in full. In APS, the only news from recent trials was negative, resulting in a recommendation not to use the direct oral anticoagulant rivaroxaban in patients with triple aPL positivity [2]. Similarly, the new EULAR/ACR classification criteria do not include a single novel laboratory test.

In our view, what the four papers have brought forward is a clearer and relatively simple concept of SLE and its management. This is not a trivial achievement, given the notorious complexity and variability of the disease and the still incomplete understanding of SLE pathophysiology. While we submit that each of the four papers is worth reading in detail, and while this certainly is a simplification that is only partly legitimate, we have taken the liberty of trying to extract the main messages in Table 1.

Following the ACR criteria originally published in 1982 [6] and the 2012 SLICC criteria [7], the 2019 EULAR/ACR criteria [4] added only non-infectious fever [8] as an entirely new clinical item. Many items had already been included in the ACR criteria and several new items entered the stage with the SLICC criteria. In fact, the EULAR/ACR criteria reduced rather than increased the number of items. Really new items include (i) ANAs now being in the position of an obligatory entry criterion, (ii) fully weighted criteria and (iii) one attribution rule for all criteria items, namely that they are to be counted only if there is no alternative explanation more likely than SLE.

In addition to taking the clinical algorithm and the test properties into account, obligatory positive ANA (ever) carries a SLICC concept a step further: instead of any immunological criterion [7], positive ANA means autoantibodies against DNA or RNA or the respective DNA or RNA binding proteins. While there are occasional patients with SLE who are ANA negative and still need treatment for lupus, the data demonstrated that positive ANA is indeed the rule in SLE. Weighted criteria were a logical consequence, both of our clinical thinking and of a first step towards this goal by the SLICC criteria; histologically proven LN already had a higher weight than

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Submitted 28 May 2020; accepted 15 September 2020

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Table 1 An attempt at extracting the main messages of the four publications

EULAR SLE recommendations, Fanouriakis *et al*. [1]	EULAR APS recommendations, Tektonidou *et al*. [2]	EULAR/ERA-EDTA LN recommendations, Fanouriakis *et al*. [3]	EULAR/ACR SLE criteria, Aringer *et al*. [4]
HCQ (≤5 mg/kg) for all SLE patients unless contraindicated	LAC, aCL[a], antiβ2GPI[a] 2×, ≥12 weeks apart	Renal biopsy (ISN/RPS) if proteinuria persistently >0.5 g/day	Positive ANA ever as entry criterion
Target remission or low disease activity with GC <7.5 mg/day	Target INR 2–3 after first venous thrombosis	Target proteinuria 50% at 6 months and <0.5–0.7 g/day at 12 months	Weighted items (2–10) in 10 domains for cut-off ≥10
Use AZA, MTX, MMF; as second step, use belimumab for organ involvement	Target INR 2–3 or INR 3–4 for arterial thrombosis (no DOACs[b]), long-term	Induction MMF (III/IV/V) or Euro-Lupus CYC (III/IV)	Count items only if no more likely alternative explanation than SLE
i.v. CYC for life-threatening disease	LMWH + LDA for obstetric APS	Maintenance with AZA or MMF (>3 years)	Count highest in each domain only
Off-label rituximab for severe refractory SLE	Heparin + GC + PE or IVIG for CAPS	Renal transplant early or dialysis/CAPD	At least one clinical item is required
Vaccination, cardiovascular risk management	LDA for asymptomatic aPL positive[b]	ACEi/ARB, vitamin D, statins, anticoagulants	Anti-dsDNA tests of ≥90% specificity only

[a]IgG or IgM in medium–high titres. [b]High-risk profile (triple-positivity). ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; antiβ2GPI: anti-β2-glycoprotein I antibodies; anti-dsDNA: antibodies to dsDNA, CAPD: chronic ambulatory peritoneal dialysis; CAPS: catastrophic APS; cv: cardiovascular; DOACs: direct oral anticoagulants; GC: glucocorticoids; INR: international normalized ratio; ISN/RPS: International Society of Nephrology/Renal Pathology Society classification; LAC: lupus anticoagulant; LDA: low-dose aspirin (75–100 mg); LMWH: low molecular weight heparin; PE: plasma exchange.

other items [7]. This also means that SLE joint involvement and highly specific antibodies to dsDNA are sufficient for the classification. The attribution rule of counting criteria only if no more likely explanation exists finally replaced previously defined exclusion criteria for various items [6, 7], given that a truly complete list would become too long to be realistic.

The main steps forward in the new EULAR recommendations on SLE management [1] are the full consensus that all SLE patients should receive HCQ, unless there are contraindications, and, even more importantly, fully adopting the treat-to-target principle in SLE [9]. Essentially adopting the safety recommendations of the American Academy of Ophthalmology, HCQ is limited to ≤5 mg/kg and screening recommendations must be implemented. The treat-to-target approach combines the goal of remission or low disease activity with reducing glucocorticoids to <7.5 mg prednisolone equivalent daily and tapering them further if possible [9]. Accordingly, if necessary for SLE control, immunomodulators or immunosuppressants should be added to HCQ.

The EULAR SLE management recommendations [1] as well as the EULAR/ERA-EDTA LN management recommendations [3] also stress the importance of prophylaxis against cardiovascular and infectious risks as well as osteoporosis. The LN recommendations specifically address the importance of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as adjunct treatment as well as of anticoagulation in patients with APS. Mainly, however, they set a relatively low level of proteinuria (≥0.5 g/day) cut-off for a renal biopsy, which stands as the most important diagnostic step, and adapt the treat-to-target approach to a 50% reduction of proteinuria within 6 months and reaching a level of 0.5–0.7 g proteinuria by 1 year.

In addition, MMF and the Euro-Lupus regimen of i.v. CYC [10] now clearly lead in induction therapy, followed by at least 2.5 years of maintenance with MMF or AZA. Finally, the APS recommendations [2] discuss the importance of high-risk autoantibody profiles (triple positivity, lupus anticoagulant, high anti-cardiolipin and/or anti-β2-glycoprotein I levels), while stressing the importance of the clinical phenotype (asymptomatic aPL carriers with or without SLE; venous, arterial or obstetric manifestations; and catastrophic APS) for therapeutic decisions.

With the advent of targeted therapies, the SLE field is now thoroughly prepared. We think that these concepts will stand, but obviously hope for even better therapies.

Funding: None.

Disclosure statement: Other than each having been part of at least one of the four EULAR projects in focus, the authors report no specific conflicts of interest for this editorial.

Data availability statement: Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and

execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

References

1 Fanouriakis A, Kostopoulou M, Alunno A *et al.* 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736–45.

2 Tektonidou MG, Andreoli L, Limper M *et al.* EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296–304.

3 Fanouriakis A, Kostopoulou M, Cheema K *et al.* 2019 update of the joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79:713–23.

4 Aringer M, Costenbader K, Daikh D *et al.* 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–9.

5 Morand EF, Furie R, Tanaka Y *et al.* Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med 2020;382:211–21.

6 Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.

7 Petri M, Orbai AM, Alarcon GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

8 Mosca M, Costenbader KH, Johnson SR *et al.* Brief report: how do patients with newly diagnosed systemic lupus erythematosus present? A multicenter cohort of early systemic lupus erythematosus to inform the development of new classification criteria. Arthritis Rheumatol 2019;71:91–8.

9 van Vollenhoven RF, Mosca M, Bertsias G *et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis 2014;73:958–67.

10 Houssiau FA, Vasconcelos C, D'Cruz D *et al.* The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–4.