of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE).

Methods A literature review was performed for manuscripts in English language on the EULAR/ACR criteria for SLE, which were published since the publication of the criteria.

Results A total of 28 different studies worldwide externally validated the EULAR/ACR criteria since their publication. These included 8,800 patients with SLE and 5,492 patients with other diseases. Cohorts differed, and included pediatric SLE and early disease (table 1). In the combined SLE population, data on anti-nuclear antibodies (ANA) could be analyzed for 7,393 patients, and 97,2% (7,185/7,393) had positive ANA. The EULAR/ACR criteria had a combined sensitivity of 93.3% (8,207/8,800) and a specificity of 93.7% (5,143/5,492). These data are close to the validation cohort data of the EULAR/ACR criteria with a sensitivity of 96.1% and a specificity of 93.4%. The slightly lower sensitivity in early SLE cohorts is in line with data from the EULAR/ACR criteria cohort, showing a sensitivity of 89% in the first year, increasing to 97% for years 1 to 3. The percentage of ANA positive patients and EULAR/ACR classification criteria sensitivity were significantly correlated (Spearman $r=0.52$, $p=0.0041$). EULAR/ACR criteria specificity relies on correctly applying their attribution rule, that items must not be attributed to SLE if there is a more likely alternative diagnosis. In Chung et al, specificity increased from 85.8% to 95.0% when attribution was correctly done. Data from the EULAR/ACR cohort show that this may be particularly relevant for lupus arthritis, were the misattribution of rheumatoid arthritis would have significant impact.

Conclusions The EULAR/ACR classification criteria have been extensively validated by groups worldwide, and the data support both their performance and their structure with ANA as an obligatory entry criterion.

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I15 TARGETING TYPE I INTERFERON IN SLE AND LUPUS NEPHRITIS

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Objective Evidence that the type I interferon (IFN) pathway plays an important role in the pathogenesis of systemic lupus erythematosus (SLE) has been mounting over the last several decades. After IFN's discovery in 1957, we grew to appreciate that it was a vital component of our host defense against viral infections. It wasn't until 1979 that its role in inflammatory diseases was subsequently recognized. In that year, investigators at the National Institutes of Health noted that approximately 71% of patients with active SLE had elevated IFN concentrations in their blood. Additional links between IFN and SLE came in the form of isolated case reports; that is, patients treated with IFN for malignancy developed illnesses that resembled SLE. A major milestone occurred in 2003 with the publication by several groups of the IFN Gene Signature (IFNGS). As the measurement of IFN blood levels was quite challenging at the time, this technology advanced both basic and clinical research.

With a link materializing between IFN pathway activation and SLE, it was only natural that this pathway be the target of therapeutic interventions in SLE. Although rontalizumab and sifalimumab, the first two monoclonal antibodies directed against interferon alpha to be evaluated in clinical trials, yielded negative and modest clinical trial results, respectively, other pursuits were undertaken that proved more fruitful. The success of anifrolumab, a monoclonal antibody directed against the type I IFN receptor (IFN alpha receptor), was attributed to the fact that all five type I IFN subtypes signal through the same receptor. The prediction was that the administration of anifrolumab would therefore result in greater inhibition of the IFN pathway compared to its predecessor, sifalimumab, which inhibited only alpha IFN and left the four other type I IFN subtypes available to interact with the receptor. In fact, IFNGS inhibition was approximately 90% with anifrolumab compared to approximately 25% with sifalimumab. The next step was to determine whether greater inhibition of the IFN pathway would translate into greater clinical responses than what was observed with sifalimumab in phase 2.

The phase 2 SLE clinical trial of anifrolumab yielded robust results and served as the foundation for the phase 3 program. While there were some hiccups in the phase 3 program, robust clinical trial outcomes in the TULIP-2 phase 3 study provided solid evidence of the effectiveness of IFN inhibition.

The anifrolumab program reaffirmed the clinical significance of type I IFN in SLE and boosted confidence that other approaches to inhibit type I IFN would prove efficacious. This presentation will review various strategies being pursued in order to block the interferon pathway in SLE and lupus nephritis.

I17 CHOOSING WISELY: WHICH BIOLOGICAL SHOULD WE USE IN WHICH PATIENT?

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Two biologicals, belimumab and anifrolumab, are currently approved for use in SLE, and are therefore supported by extensive phase 3 clinical trials, while some others are supported by more limited data but may be used off-label. For the clinician an important practical question is which biological to choose for the individual in whom a biological is, indeed, needed to control the disease and achieve better outcomes.

Important considerations to guide such choices are:

- for belimumab, anti-DNA (+) status and low complement indicate a greater treatment effect
- for anifrolumab, specific benefits with respect to cutaneous manifestations of SLE have been demonstrated
- no other subsets of patients have been identified as particularly likely to respond to these two biologicals, but some subsets may be less likely to benefit
- belimumab is approved for both SLE in general and for lupus nephritis, and for use in pediatric patients
- the side effect profiles of belimumab and anifrolumab are dissimilar and may therefore guide treatment choice in individual cases
- the search for better biomarkers to guide therapy continues