Methods We screened 463 epigenetic regulatory genes using a siRNA library in a high-throughput ISRE-luciferase assay. Q-PCR and Western blot were used to study the function of targeted genes.

Results Among those genes which significantly enhanced or inhibited ISRE activity, CDK1 had a differential expression in PBMCs and renal biopsies between SLE patients and healthy controls and was positively correlated with "IFN scores" and disease activities of SLE patients. We revealed that the expression of ISGs and phosphorylation of STAT1 could be reduced by knocking down CDK1, while over-expression of CDK1 produced an opposite effect. As specific inhibitors of IFN pathway has emerged as a promising treatment for SLE and CDK1 inhibitors are being on trial for some types of cancer, we wondered whether CDK1 inhibitor could be a potential repositioning drug for SLE. We found a CDK1 inhibitor, RO-3306, could alleviate FN in PBMCs from 5 SLE patients who had high IFN scores. We found that RO-3306 significantly reduced ISGs expression in these cells. Our preliminary data further showed that RO-3306 could reduce proteinuria in SLE mouse model.

Conclusions We proposed that CDK1 is a novel positive regulator of IFN signalling pathway, over-expression of CDK1 in SLE might contribute to the over-activated IFN signalling and inhibition of CDK1 could be used to interfere abnormal IFN signalling in SLE.

A MOLECULAR SIGNATURE BASED ON IFN GENE SIGNATURE AND SEROLOGY DEFINES TWO POPULATIONS OF PATIENTS WITH DIFFERENT BASELINE DISEASE ACTIVITY

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Background and Aims Randomised controlled trials in SLE have shown that response to treatment is influenced by baseline disease activity. The current investigation used objective molecular and biochemical baseline parameters to characterise SLE patients in two large multinational trials (n=2262 patients).

Methods Patients were categorised with four dichotomous baseline parameters. SLE(+) was defined by any of the following: IFN signature (high), anti-dsDNA (+), C3 (low) and/or C4 (low). SLE(-) required all of the following: IFN signature (normal), anti-dsDNA (-), C3 (normal) and C4 (normal).

Results Baseline RNA transcript data were available for 1747 of 2262 patients. When IFN status was combined with the serology criteria, 1500 (86%) were classified as SLE(+) and 247 (14%) were classified as SLE(-). At baseline, SLE(+) patients had significantly lower mean SLEDAI scores (8.3) compared to SLE(+) (10.7). Baseline SLEDAI <10 was observed in 72% of SLE(-) compared to 38% of SLE(+). The proportion on corticosteroids at baseline was 49% in SLE(-) compared to 78% in SLE(+); the proportion on immunosuppressants at baseline was 31% in SLE(-) compared to 44% in SLE(+). In the US, 22% were SLE(-) compared to 10% for Latin America, 7% for Europe, and 5% for ROW.

Conclusions A subset of clinical trial patients was identified using biochemical and molecular markers with high sensitivity for SLE. Seronegative SLE patients with normal IFN gene signature had lower disease activity and were taking less background medication at baseline, two factors which have been negatively associated with response to treatment in some previous trials.
reveals various clinical course and therapeutic responsiveness according to the clinical and serological subsets. Some myositis-specific autoantibodies (MSAs) are useful markers for the classification of ILD in myositis and give useful information for predicting the prognosis and determining treatment.

Anti-aminoacyl-tRNA synthetases are closely associated with a common clinical manifestation, termed “anti-synthetase syndrome” including high prevalence of ILD. ILD in patients with anti-synthetase shows a similar clinical course with a favourable response to therapy but frequent recurrences. Therefore, the concomitant use of glucocorticoids and immunosuppressive drugs is recommended from early stage of the disease.

Anti-MDA5 antibody was reported to be associated with clinically amyopathic dermatomyositis (CADM) with rapidly progressive ILD, especially in eastern Asian population. Because of a very poor life prognosis, the intensive immunosuppressive therapy against ILD from early stage is recommended using the combination of high dose glucocorticoids, calcineurin inhibitors and intravenous cyclophosphamide. We have experienced the effectiveness of plasmapheresis in some anti-MDA5-positive patients with intractable ILD, suggesting a possible pathogenicity of anti-MDA5 antibody.

Thus, ILD in myositis is dependent on the autoantibodies, therefore it is important to know the profiles of MSAs in PADM patients. Recently, we established the ELISA systems for anti-synthetase and anti-MDA5 antibodies, which are as efficient as the standard immunoprecipitation assays. These systems enable easier and wider use in the diagnosis and therapeutic decision of patients suspected to have myositis and ILD.

The most common SLEDAI organ systems involved at base ment in SLEDAI score, coupled with successful trial completion, concomitant medication adherence and trial completion. At least one SLEDAI manifestation with low prevalence and high score (≥4 pts) was present in 18.1% and 17.2% of patients in Trials 1 and 2, respectively. SRI-5 response rates for these patients were higher, regardless of treatment assignment.

Background and Aims SRI is a composite endpoint used in many SLE trials. The current investigation sought to identify those SRI components that drive response.

Methods This study evaluated data from two large multinational trials that used SRI-5 as primary endpoint (n=2262 patients).

Results The overall SRI-5 response rate was 32.8%. Non-response due to lack of a 5-point SLEDAI improvement, comrailed violation or dropout were observed in 31%, 16.5% and 19.1%, respectively. In contrast, only 0.5% (11/2262) of patients failed to respond due to deterioration by BILAG or PGA, once achieving the first three components.

The most common SLEDAI organ systems involved at baseline were mucocutaneous (90.6%), musculoskeletal (82.9%) and renal (71.6%). The 6 other SLEDAI-defined organ systems were active in ≤11% of patients.

At least one SLEDAI manifestation with low prevalence and high score (≥4 pts) was present in 18.1% and 17.2% of patients in Trials 1 and 2, respectively. SRI-5 response rates for these patients were higher, regardless of treatment assignment.

Conclusions The SRI-5 response is driven by SLEDAI improvement, concomitant medication adherence and trial completion. Patients with less frequent, more severe manifestations had high placebo response rates. A simple dichotomous improvement in SLEDAI score, coupled with successful trial completion and medication stability, provides a more efficient, clinically relevant approach to assess outcome.