

asked ourselves if the genetic associations would differ with the new cluster stratification.

Methods For drug analysis we used two described sets of patients (1) selecting gene expression data of one visit/patient with active SLE (SLEDAI>5). Patient gene signatures were compared to drug derived gene signatures from CLUE database, giving a connectivity score. A negative score reflects inverse patterns between two signatures implying the drug may revert the disease-signature while a positive score would simulate disease. The magnitude of the score reflects the potential efficacy of the drug. Genetic data was performed in independent sets of individuals, focusing on the HLA.

Results Patient stratification based on drug connectivity scores revealed the same cluster structure described (correlation between neutrophil/lymphocyte ratio and SLEDAI dNLR $p=1 \times 10^{-7}$), implying that differential treatment depends on the cluster to which patients belong. Although drugs commonly used in SLE did not show the best scores, we found different values for each cluster suggesting that expression of target genes may provide insight in the prioritization of compounds.

We next constructed a model to classify patients using cluster information to inform on drug use and predict nephritis applied to 3 new longitudinal cohorts. A meta-analysis showed a significantly higher incidence of nephritis in patients classified to a neutrophil-driven cluster (2). In addition we observed differences in the genetic associations to disease in the HLA region depending on the clusters.

Conclusions Drug patterns reverting disease gene expression follow the cell-specificity of the disease clusters and provide a clinically useful model to treatment selection and nephritis. Clustering, at least in one case is also guided by the genetic contribution to disease.

14 PLANNING AND MANAGEMENT OF LUPUS NEPHRITIS IN PREGNANCY

David P D'Cruz. Louise Coote Lupus Unit, Guy's and St Thomas' Hospitals, London UK

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Background SLE primarily affects young women in their child-bearing years and lupus nephritis is a common complication that often develops early in the disease course. Patients with lupus nephritis are at increased risk of fetal and maternal morbidity.

Methods Careful pre-pregnancy counselling is essential and should involve a multidisciplinary team with experience of managing high risk pregnancies. Careful management of active lupus nephritis aiming for complete clinical remission and optimising treatment to safely discontinue fetotoxic therapies is essential prior to discussing pregnancy. While these aspects are being managed, effective contraception is vital to avoid unplanned pregnancy with active lupus nephritis. The broader picture including previous obstetric history, assessment for antiphospholipid antibodies and neonatal lupus syndrome in Ro/La positive women also needs to be considered. Patients with lupus nephritis, even when in remission need very close monitoring throughout pregnancy and the post-natal period.

Results Data in the literature suggests that lupus flares including lupus nephritis flares, hypertension and pre-eclampsia may occur in up to 25% of patients. Lupus nephritis flares in pregnancy increase the risk of renal impairment, intra-uterine

growth restriction, premature delivery and fetal morbidity including stillbirths and neonatal deaths and rarely maternal mortality.

Conclusions With careful management, women with lupus nephritis can have successful pregnancies.

15 DEFINING LUPUS: CHANCES AND CHALLENGES BASED ON THE EULAR/ACR CRITERIA

Martin Aringer. Division of Rheumatology, Department of Medicine III, University Medical Center and Faculty of Medicine TU Dresden, Dresden, Germany

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Background The EULAR/ACR classification criteria for SLE have introduced three new concepts. One, ANA, with their high sensitivity, but low specificity, were re-positioned to an entry criterion. Two, all criteria items are now attributed specific weights, and this often means that two criteria, such as arthritis and antibodies to double-stranded DNA (dsDNA), are sufficient to reach the 10 point classification line. Three, instead of long lists of exclusion criteria, there is one attribution rule for all items, namely that criteria are only to be counted for SLE if there is no more likely alternative cause - such as rheumatoid arthritis for arthritis in an anti-CCP positive patient. All these concepts have individually led to discussions and misunderstandings.

Results Although ANA need to be positive only once ever, it is clear that this entry criterion still excludes patients who were always ANA negative. ANA negative SLE exists, but is uncommon, which makes this much less of a problem for classification than for diagnosis, and it is important to re-iterate that the diagnosis must be possible independent of classification criteria. In poor countries, ANA testing may be a problem, but worldwide availability of such a test must be an obvious goal. Test quality has also been discussed. Critically, not all ANA substrates had adequate sensitivity, and this has to be resolved.

For the lupus specific antibodies to Sm and dsDNA, with a relative weight of 6 points, specificity is the more critical issue. Many anti-dsDNA tests have insufficient test specificity, so that anti-dsDNA can only be counted if positive in a test with at least 90% specificity against appropriate disease controls. This is typically true for Crithidia and Farr assays, but not for many of the high throughput tests of today. Clinicians will have to be aware of the test characteristics of the anti-dsDNA tests they have available. SLE classification needs knowledge of autoantibody testing, and appropriate training of physicians will be key.

The attribution rule probably is the most challenging concept. In essence, criteria should not be counted for the classification of SLE if not accepted for expert diagnosis. In this sense, attribution is very close to the clinical process of diagnosis, as hoped for, but this needs knowledge on typical findings of other autoimmune diseases that are relevant differential diagnoses to SLE, such as primary anti-phospholipid syndrome or Sjögren's syndrome. Appropriate attribution may be troublesome in data bases, and not following the attribution rule with diligence will automatically diminish the specificity of the new criteria. Above attribution, a misdiagnosis of for example mucocutaneous items, such as mistaking Rosacea for malar rash, will also cause trouble. Again, appropriate training will be necessary.