

Invited talks

11 WHY SHOULD ALL PATIENTS TAKE HYDROXYCHLOROQUINE?

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Background Hydroxychloroquine (HCQ) has been used in the therapy of SLE for more than 50 years. The importance of this drug has been increasingly recognised within the last 10 years.

Methods A critical review of the literature as well as the author's point of view will be offered.

Results Recent studies have confirmed the effects of HCQ in improving survival, decreasing SLE flares, reducing damage accrual and infections. In addition, beneficial effects in pregnant women include a reduction in preterm delivery and fetal growth restriction, as well as a reduction in the risk for cardiac neonatal lupus in babies born to anti-Ro-positive mothers. The addition of Mepacrine to therapy including HCQ has proven very effective in SLE patients with refractory skin and/or articular activity.

The risk for serious side effects is low even after prolonged use of the drug. Maculopathy is the most feared side effect of HCQ. The recent availability of sensitive screening techniques (particularly, the spectrum domain-optic coherence tomography, or SD-OCT) help capture cases of early (i.e. reversible) toxicity, but also increases the probability of discontinuation of the drug. Recent guidelines suggest that daily doses >5 mg/kg/d of HCQ are the main predictor of toxicity. Some authors have questioned this recommended reduction of the usual dose and the utility of blood levels of HCQ to predict retinal toxicity has also been proposed.

In the author's experience, doses of 200 mg/d are sufficient for the majority of patients. Indeed, in our cohort studies showing protection of HCQ against thrombosis, infections, cancer and improved survival, most patients were treated with 200 mg/d, which reassures the efficacy of such doses.

Conclusions HCQ is the background therapy of SLE and should be recommended long-term in all patients without contraindications. Doses of 200 mg/d are effective and safe and should be considered the standard of care. The addition of Mepacrine potentiates the effects of HCQ in patients with non-responsive skin and/or articular activity. HCQ must not be stopped during pregnancy. Screening for retinal toxicity using sensitive techniques, including SD-OCT must be assured following recent recommendation. In addition, it is very important that a skilled and experience team of ophthalmologists, in close contact with lupus doctors, take care of the screening, in order to avoid unnecessary discontinuations of this essential drug.

12 HOW TO OPTIMIZE USE OF GLUCOCORTICOIDS IN SLE

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Background Glucocorticoids (GC) are a mainstay therapy for disease activity in Systemic lupus erythematosus (SLE) patients.

In addition to induction of remission, many SLE patients receive long-term maintenance treatment with GC. On the reverse side, it is well established that GC use results in important adverse effects that are directly proportional to the dose and duration of GC treatment. These includes increased risk of infections and accrual of irreversible organ damage, that are major contributors to the morbidity and mortality of SLE patients. Hence, risk-benefit must be carefully considered for optimal use of GC and improve outcomes of SLE patients.

However, evidence base is still scarce for establishing standardized approaches to GC initiation, tapering and withdrawal for optimal management of SLE. As a result, clinical practice regarding use of GC in the treatment of SLE patients is wildly heterogenous.

Methods This review will focus on evidence and recommendations to optimize use of GC, which is a critical unmet need in the management of SLE.

Results Induction treatment of moderate and severe inflammatory lupus manifestations is the major indication for GC in SLE. In patients with milder manifestations, such as localized mucocutaneous lesions, arthralgias and mild cytopenia, hydroxychloroquine is the mainstay of treatment and use of systemic GC might not be needed. Common mild complaints, including arthralgia, myalgia, fatigue, headache or mild cognitive symptoms can be frequently due to non-inflammatory comorbidities, that must be differentiated from lupus flares and do not benefit from GC treatment. In treat-to-target strategy for SLE management, tapering of GC to ≤ 7.5 or preferably ≤ 5 mg/day of prednisone is an important objective, as it is associated with improved outcomes. Use of low dose prednisone in maintenance treatment of SLE patients is controversial. A recently published clinical trial showed that in SLE patients with quiescent disease, withdrawal of 5 mg/day of prednisone was associated with an increased risk of flare, however there was no significant difference in the risk of severe flares.

Conclusions Minimization of exposure to GC, along with achieving a stable remission or at least a low disease activity state are central targets in the management of SLE. For this purpose, it is fundamental a judicious use of GC for treatment of disease activity, and to optimize use and adherence to hydroxychloroquine and immunosuppressant therapy in order to achieve successful tapering and whenever possible the withdrawal of GC.

13 USING PATIENT STRATIFICATION TO DEFINE GENETICS OF DISEASE

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Background Systemic lupus erythematosus (SLE) is a heterogeneous disease with unpredictable patterns of disease activity measured using mostly the SLEDAI. However, patients with similar SLEDAI scores may have different prognosis and molecular abnormalities. We reported the longitudinal stratification of SLE into 3 clusters based on correlation between gene expression and SLEDAI (1). Each cluster showed differences in molecular pathways involved, clinical manifestations, and how cell populations evolved with activity. In addition we

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

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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

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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.