Session 1: Treatment dilemmas

01 SHOULD WE VACCINATE ALL SLE PATIENTS AGAINST PAPILOMAVIRUS AND HERPES ZOSTER?

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The dysregulated host immune system and treatment with immunosuppressive medications predisposes patients with systemic lupus erythematosus (SLE) to increased risk of infections such as Human Papilloma Virus (HPV) and Herpes Zoster (HZ).

HPV causes genital warts and malignancy including cervical, penile, and anogenital cancers. In a recent meta-analysis, the prevalence of HPV in SLE was found to be significantly higher than controls, with an odds ratio (OR) = 2.87.¹

SLE is associated with the highest rate of HZ infection in all age strata below 70 years, with an age-adjusted incidence of 12.0/1000 person-years (hazard ratio 1.7).² The use of cyclophosphamide and mycophenolate mofetil with glucocorticoids in lupus is associated with a seven-fold increase in HZ reactivation. Similarly, the use of anifrolumab in SLE clinical trials was associated with OR = 4.089 of HZ infection.³

Immunization against common pathogens can potentially be very beneficial in preventing infections in SLE. However, safety and efficacy of vaccines for patients with SLE generate perennial controversy. Concerns are fueled by case reports of *de novo* development of autoimmune disease or flares of existing autoimmune disease after administration of vaccines. In addition, theoretical concerns about inadequate host immune responses to vaccines raise doubts about their effectiveness in protecting patients with SLE from infection.

Overall, HPV vaccines seem to be safe and immunogenic in patients with SLE. A study of 210 patients with SLE, HPV vaccine was found to be immunogenic in ~90% of patients with no serious side effects or increased lupus flare at one-year follow-up.⁴ The use of cyclophosphamide was associated with low rates of HPV seroconversion. The live-attenuated HZ vaccine was also found to be safe and immunogenic with no increase in incidence of herpes zoster in patients with SLE on milder immunosuppressants.^{5, 6} There is still no data regarding the efficacy of the subunit and inactivated HZ vaccines in SLE patients, but studies in other immunocompromised populations showed it to be safe and immunogenic. Vaccination against HPV and HZ in SLE patients resulted in significantly lower rates of infections.

Overall, HPV and HZ vaccines appear to be safe and effective in patients with stable lupus on low intensity immunosuppressants.

Learning Objectives

- Describe the high incidence of human papillomavirus and herpes zoster infections in patients with SLE
- Address concerns associated with vaccination administration in SLE
- Explain the safety, efficacy, and limitations of data from studies of HPV and HZ vaccines in SLE patients

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02 HYDROXYCHLOROQUINE MYOPATHY: CARDIAC AND SKELETAL MUSCLE TOXICITY

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Antimalarial myopathic toxicities may involve both skeletal and cardiac muscles. In skeletal muscle it is a deposition myopathy and in cardiac muscle there may be a direct chemical action toxicity or a deposition myopathy.

In skeletal muscle there are isolated case reports of clinical myopathy and two prospective studies, one of 119 cases and the other of 21 cases.^{1, 2} Both showed $\pm 19\%$ abnormal muscle enzymes. Clinical weakness was very uncommon but biopsies in 15 patients showed classic EM findings of antimalarial toxicity. All patients improved with cessation of antimalarials.

In chemical toxicity of cardiac muscle, antimalarials may cause QTc prolongation. This is based on isolated case reports. In one cross sectional case series of 90 patients there was no difference in QTc between those on antimalarials and those not.³ There are no reports of sudden death in lupus patients starting antimalarials. Perhaps the more significant findings are related to the deposition of antimalarials in cardiac muscle resulting in antimalarial induced cardiomyopathy (AMIC). Clinical, serologic, imaging and biopsy features of this complication will be described in 8 patients recently seen in the University of Toronto Lupus Clinic.⁴ A systematic review of 47 patients with biopsy proven AMIC will be presented.⁵ Features of AMIC include morphologic/structural changes (biventricular/septal hypertrophy, bi-atrial enlargement); functional defects (impaired systolic and diastolic function); conduction disorders (RBBB, LAFB, cAVB/SSS); elevated biomarkers (troponins [cTnI], BNP, CPK). In 151 lupus patients with no prior history of heart disease we found 16 (10.6%) had abnormal cTnI and/or BNP.⁶ Of these six were diagnosed with AMIC, five with other diagnoses and five do not yet have a definite diagnosis. Cardiac biomarkers should be ordered in patients who are older, have a decreased eGFR, have elevated CK without clinical myositis, and who have taken antimalarials for more than 5 years.

Learning Objectives

- Describe antimalarial muscle toxicity in skeletal and cardiac muscle
- Discuss the possible association between antimalarial treatment and QTc prolongation and its possible consequences
- Describe antimalarial deposition in cardiac muscle and its consequences
- Differentiate the role of cardiac biomarkers in the early detection of antimalarial induced cardiomyopathy

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03

LOW DOSE ASPIRIN IN APL-POSITIVE PATIENTS: ARE WE TREATING THE PATIENT OR THE DOCTOR?

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Patients with antiphospholipid antibodies (aPL) are at increased risk for arterial or venous thrombosis. There is, however, significant heterogeneity among patients according to clinical and laboratory features. Therefore, two therapeutic modalities can be discussed for primary prevention of thrombosis in patients: (1) primary prophylaxis in all aPL patients or (2) only in selected high-risk patients. Because aPL are often diagnosed in patients with systemic lupus erythematosus before occurrence of a first thrombosis, primary prophylaxis should be specifically discussed in this setting.

Risk for thrombosis in lupus patients may be increased by additional clinical risk factors, in particular hypertension. Laboratory profile is also important: lupus anticoagulant, double (any combination of lupus anticoagulant, anticardiolipin antibodies or anti-b2 glycoprotein I antibodies) or triple (all three subtypes) aPL positivity, as well as the presence of persistently high aPL titres indicate high risk patients. Specific risk scores may be helpful such as the global antiphospholipid syndrome score (GAPSS).

Observational data indicate that low dose aspirin reduces the risk of first thrombosis in aPL patients, particularly in those with lupus (by 50%) with a low bleeding risk. To improve the risk:benefit ratio, prescribe aspirin in patients with high-risk profiles and low bleeding risk.

Treatment failure may be due to aspirin resistance (insufficient dosage, poor absorption or drug interaction) or poor treatment adherence (long term prophylactic treatment in

young patients) of which the attending physician must be aware.

In summary, prophylactic low dose aspirin in aPL positive lupus patients should be considered taking into account thrombotic and bleeding risks. Because of its long-term objectives, this treatment should be carefully explained and discussed with the patient before taking a shared decision.

Learning Objectives

- Explain when primary prophylaxis should be used for APL
- Describe the risk factors for thrombosis in patients with lupus
- Discuss optimal treatment options for thrombosis risk reduction in patients with aPL

Session 2: The role of interferons in SLE

04

BIOLOGY OF INTERFERONS IN SLE: INSIGHTS FROM LONGITUDINAL DATA ANALYSIS

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Type I interferons (IFNs), including IFN- α , IFN- β , IFN- ω and IFN- κ , represent an essential host defense mechanism stimulated by virus infection.^{1–4} In that setting, type I IFN is tightly regulated with duration of expression limited to several days. When its production is sustained, its protean effects on immune cell function can be damaging. Activation of the type I IFN pathway, typically defined by elevated expression of type I IFN-inducible gene transcripts or their protein products, is a feature of nearly all children diagnosed with systemic lupus erythematosus (SLE), as well as the majority of adult lupus patients. Taken together with insights from murine models, studies of lupus patients have supported the conclusion that type I IFNs comprise a family of pathogenic mediators that contribute to autoimmunity, inflammation and ultimately tissue damage in patients with SLE and some other systemic autoimmune diseases, particularly primary Sjogren's syndrome and dermatomyositis.

Coordinated expression of type I IFN-stimulated genes is a feature of most patients with SLE, but the relationship of the IFN signature to disease activity has been debated. In addition, the inducers of IFN and the molecular pathways and signaling molecules that result in IFN production have not been well defined. Endogenous nucleic acids have been identified as the relevant drivers of type I IFN production, but the specific features of those nucleic acids have not been well characterized. It is not apparent whether the endosomal toll-like receptors or cytosolic nucleic acid sensors are most relevant to IFN expression in individual patients. Finally, the mechanisms that regulate activation of the IFN pathway – or fail to regulate that pathway in some lupus patients – have not been well defined. To gain insight into these issues, we collected extensive longitudinal clinical, serologic, proteomic and gene expression data to assess the correlates of IFN pathway activation, and to establish new hypotheses regarding the relationship of autoantibody specificity and environmental exposures to production of IFN and induction of IFN-stimulated genes.

Analysis of proteomic and gene expression data collected for up to 4 years on individual patients was analyzed to