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 understand temporal patterns among relevant autoantibodies and the IFN signature in relation to disease flares. Our data suggest a potential role for microbial triggers in driving the immune system activation that leads to disease flares and support activation of the type I IFN as highly associated with disease flare in many patients.

Learning Objectives

- Describe potential mechanisms of type I IFN induction in SL
- Describe individual temporal patterns in immune system activation based on longitudinal patient data
- Explain possible interpretations of longitudinal patient data with regard to triggers of lupus flare

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05 HOW INTERFERONOPATHIES INFORM SLE PATHOGENESIS

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Type I interferon (IFN) is a potent substance. As such, the induction, transmission and resolution of the type I IFN-mediated immune response are tightly regulated. The type I interferonopathies represent discrete examples of a disturbance of the homeostatic control of this system due to Mendelian mutations, and their molecular definition has the potential to dissect fundamental aspects of IFN control in the human context. Of note, the recognition of type I interferonopathies is becoming of increasing clinical importance as treatment options are developed based on an understanding of disease pathology and innate immune signaling. Definition of the type I interferonopathies indicates that autoinflammation can be both IFN and non-IFN related, and that a primary disturbance of the innate immune system can 'spill-over' into autoimmunity in some cases. Indeed, the fact that a number of non-Mendelian disorders, particularly systemic lupus erythematosus (SLE) and dermatomyositis, are also characterized by an upregulation of type I IFN signaling suggests the possibility that insights derived from this work will have relevance to a broader field of clinical medicine.

Learning Objectives

- Describe the phenotypic breadth of the type I interferonopathies
- Describe the molecular basis of the type I interferonopathies
- Describe the status of interferon signalling in the type I interferonopathies
- Describe the clinical link between the type I interferonopathies and SLE
- Describe the link between the molecular pathology of the type I interferonopathies and SLE

06 INTERFERON INHIBITION AND THE FUTURE MANAGEMENT OF SLE

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Type I interferon (IFN) is the term for a family of cytokines acting through a common receptor, known as IFNAR. Though functions are diverse, broadly speaking IFNs act in the innate immune system, providing rapid early host response to viral infection. Viruses activate IFN production largely through activating nucleic acid sensors including toll-like receptors (TLRs) 7–9 as well as other intracellular pathways, which have evolved to detect the presence of nucleic acids in the cytoplasm. Ligation of IFNAR leads to a cascade of inflammatory responses and enhances activation of the adaptive immune system.

It is now understood that these pathways of response to nucleic acid can be activated in diseases ranging from hereditary interferonopathies to acquired autoimmune interferonopathies, of which SLE is the archetype. Evidence of activation of the IFN system through increased expression of sets of IFN-regulated genes, known as the IFN signature, was first detected in SLE over 20 years ago. Other evidence for the role of IFN in SLE includes exacerbation of animal models of lupus by IFN treatment and induction of lupus-like clinical phenotypes in humans treated with IFN for other diseases.

Early clinical trials of IFN-blocking therapies had limited success, associated with incomplete suppression of the expression of IFN signatures. More recently, a monoclonal antibody to IFNAR, anifrolumab, demonstrated efficacy in a Phase 3 trial, after prior success in Phase 2 and positive results against all but the primary endpoint in another Phase 3 study. [1–3] Broadly, anifrolumab treatment resulted in reduced disease activity, improved skin, joint and flare outcomes, and increased rates of glucocorticoid tapering, with acceptable safety notwithstanding included increased rates of herpes zoster reactivation.[4]

The potential applications of IFN blocking treatments in the management of systemic lupus erythematosus (SLE) driven by this evidence base will be explored.

Learning Objectives

- Describe the biology of type I IFN in autoimmune disease
- Discuss the evidence for the role of type I IFN in the pathogenesis of SLE
- Explain early clinical trial data supporting the role of type I IFN in SLE
- Describe the efficacy and safety of anifrolumab in the treatment of SLE
- Discuss future directions in IFN inhibition in SLE

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