Symposium 5 - Autoimmune Diseases

IGG4-RELATED DISEASE

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IgG4 related disease was recognized as a unified disease entity only 15 years ago. Awareness of IgG4 related disease has increased worldwide since then, and specialists are now familiar with most of its clinical manifestations. Involvement of the pancreato-biliary tract, retroperitoneum/aorta, head and neck, and salivary glands are the most frequently observed disease phenotypes, differing in epidemiological features, serological findings, and prognostic outcomes. In view of this multifaceted presentation, IgG4 related disease represents a great mimicker of many neoplastic, inflammatory, and infectious conditions. Histopathology remains key to diagnosis because reliable biomarkers are lacking. Recently released classification criteria will be invaluable in improving early recognition of the disease.

IgG4 related disease is highly treatable and responds promptly to glucocorticoids, but it can lead to end stage organ failure and even death if unrecognized. Prolonged courses of corticosteroids are often needed to maintain remission because the disease relapses in most patients. Rapid advancement in our understanding of the pathophysiology of IgG4 related disease is leading to the identification of novel therapeutic targets and possible personalized approaches to treatment.
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HARMONISATION OF AUTOIMMUNE TESTING

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The detection and quantification of autoantibodies should be an area of diagnostics where we as clinicians and scientists should strive for accuracy. We should be able to provide robust harmonised results to enable optimum care of patients with autoimmune diseases. Over the last 10 years, the IFCC working group/committee for Harmonisation of Autoantibody Testing has worked to: i) identify the main causes of variability in autoantibody tests, ii) identify autoantibodies where a certified reference preparation could reduce inter assay variability and iii) collaborate with the JRC to prepare certified reference materials for the identified autoantibodies. Many groups were included in the process; expert scientists, clinicians, laboratories and a large number of diagnostic companies. The first two materials prepared were for IgG antibodies to the neutrophil enzymes myeloperoxidase and proteinase 3 (ERM-DA476/IFCC, and ERM-DA483/IFCC respectively) that are important in the diagnosis and monitoring of patients with ANCA (anti neutrophil cytoplasmic antibody) associated vasculitides. Both materials are commutable and fulfil the requirements of certified reference materials. Unfortunately, despite the major diagnostic companies participating in the evaluation of these materials, to date, no-one has calibrated their assays using them and the variability of these clinically critical tests remains very high. ERM-DA477/IFCC for IgG anti beta-2 glycoprotein 1 is recently available and the production of reference materials for coeliac antibodies and IgG antibodies to glomerular basement membrane are in progress. However, the wider interest in harmonisation or standardisation of autoantibody testing is passive; we need people to take an active role in the adoption of available reference materials. We need to promote the goals of the International Organisation for Standardisation (ISO), the Joint Committee for Traceability in Laboratory Medicine (JCTLM) and the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) in using internationally recognized, certified and traceable measurement standards where they are available. The overall aim is to reduce the variability in autoantibody testing to enable better patient care.
It has long been known that the complement system is activated in autoimmune diseases. More recently, pre-clinical and clinical studies have also revealed that this part of the immune system is activated in diseases not traditionally thought of as immune-mediated, including ischemia/reperfusion injury, neurodegenerative diseases, and cancer. Although the complement system is activated in such a broad range of diseases, the mechanisms of activation vary. Specific diseases involve activation through each of the three activation pathways: classical, alternative, lectin. Furthermore, the system generates a variety of pro-inflammatory protein fragments. Because of this complexity, therapeutic strategies for blocking this system should be based on understanding of the underlying mechanisms of disease.

Eculizumab is a monoclonal antibody to complement C5 that has been approved for treatment of several diseases. Several other anti-complement drugs have been recently approved, including a C5a receptor antagonist, a small molecule inhibitor of C3 activation, and a monoclonal antibody to C1s. In addition, many new complement inhibitory drugs are in clinical development. This expanding repertoire of anti-complement drugs raises the possibility of using drugs that are well-matched to the disease pathophysiology. Multiple clinical trials are now underway testing these new drugs in disease. As these trials are completed, it is likely that additional complement inhibitory drugs will enter the clinic.