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Mechanisms of modern immunomodulation Clinical aspects

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Professor Abinun is working in Great North Children's Hospital in Newcastle upon Tyne as a consultant in Paediatric Immunology and Infectious Diseases. His main interests and research projects lie in Primary Immunodeficiencies (PID), Haematopoietic Stem Cell Transplantation (HSCT) and Paediatric Rheumatology/Autoimmune Disorders.

In his fascinating presentation he first gave the audience a quick review of the differences in innate (monocytes, natural killer cells, polynuclear neutrophils; mucosal epithelial and endothelial cells; complement, cytokines and chemokines) and adaptive (T and B lymphocytes) immune system. The first typically stands for general/acute inflammation and activation whereas the second represents a specific (antigen) and protective (memory) answer. This leads to the thought that susceptibility to infections, autoimmunity, malignancy, auto-inflammation and immunosenescence are all kind of an «immune system failure».

After that, he highlighted the immunomodulation processes, in which an immune response is altered to any desirable level, naming potentiation (e. g. vaccines, tumor immunotherapy), suppression (e. g. autoimmunity, allergy, graft «manipulation») and induction of tolerance (e. g. stem cell transplantation).

Illustrating the clinical potential of different immunomodulation therapies with «real life case presentations», he reviewed the example of biologic response modifying therapies, cytotoxic therapy and HSCT for juvenile idiopathic arthritis (JIA). In 5–10% JIA is refractory to conventional therapy (NSAIDs, glucocorticoids, methotrexate, and biologic therapies), poor prognostic factors are systemic or polyarticular onset, polyarticular course and active systemic disease at 6 months. Glucocorticoids inhibit the production of inflammatory mediators, inflammatory cell migration and promote cell death, but with a variety of (serious) side-effects. Binding of adenosine to A2 and A3 receptors is (probably) one of the important anti-inflammatory mechanisms of methotrexate action. Cytotoxic drugs such as cyclophosphamide can cause serious infections and increased death rate. So he asks the question if this disease would be curable with a tailored therapy. And he discussed the autologous versus allogeneic haematopoietic stem cell transplantation (HSCT), where the latter had shown early encouraging results with improvement of rheumatological parameters, better survival rate and drug-free remission (cure). With autologous HSCT we create prolonged lymphopenia, eliminate autoreactive T-effector cells, long-living plasma cells and antigen presenting cells, and in the long-term we increase T-regulatory cells, restore thymic function, normalize T-receptor repertoir, reduce auto-antibodies skewing the balance from autoimmunity versus tolerance. Both autologous and allogeneic HSCT are associated with significant morbidity (infection and graft versus host disease, respectively) but the transplantation related mortality rate seems to «equel out» (higher risk with T cell depletion procedure in the autologous setting vs. «reduced intensity conditioning» protocols and better donor selection in allogeneic HSCT).

Related to this he further discussed the cytokine cascade and hypercytokinemia as a potentially fatal immunologic reaction consisting of a positive feedback loop between cytokines and immune cells in primary haemophagocytic lymphohistiocytosis and the secondary form seen in systemic onset JIA, the macrophage activation syndrome (MAS). Here he discussed the options of modulating the inflammatory cascade with combined therapies, including for example IL-1, TNF-alpha and IFN-gamma blockers, and the role of allogeneic HSCT as a potential cure.

Closing his talk staying with the topic of more specific immunomodulatory treatment for refractory Kawasaki-disease vasculitis, he discussed the data and case presentations supporting the notion that if we could block the inflammatory pathway earlier and more accurately (e. g. corticosteroids, tumor necrosis factor inhibitors, calcineurin inhibitors, IL-1 blockers, statins) we could better prevent the development of devastating coronary artery aneurysms.

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