of the anti-inflammatory cytokine IL-10. IL-10 Treg/Tr1 cells suppress dendritic cell maturation, prevent Th cell differentiation and create a negative feedback loop for Th driven immune pathology. Tolerance induction involves upregulation of transcription factors controlling IL-10 and inhibitory receptors limiting T cell signalling. Results from clinical trials of peptide immunotherapy will be discussed.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.7209

SATURDAY, 17 JUNE 2017

Reverse translation - learning from clinical trials in SLE, Sjögren's and APS

SP0152 LEARNING FROM CLINICAL TRIALS IN SYSTEMIC LUPUS ERYTHEMATOSUS

D.A. Isenberg. *University College London/University College Hospital London, London, United Kingdom*

An enormous sense of frustration has surrounded the results of clinical trials in patients with systemic lupus erythematosus (SLE). A steady stream of trials including those studying the effects of Epratuzumab, Abatacept, Rituximab, Tabalumab and Silfalimumab have failed to meet their endpoints. Even though Benlysta (which blocks the B-cell activating factor BAFF) did meet its endpoints, it only demonstrated a difference of around 10% between the Benlysta-treated and placebo-treated arms in trials involving over 800 patients.
However, there are some bright spots on the horizon. Trials comparing the use of Mycophenolate with other classic immunosuppressive drugs clearly showed it to be as good as Cyclophosphamide in getting patients into renal remission and demonstrated its superiority in maintaining that remission compared to Azathioprine[(1)]. The use of Atacicept which blocks two B-cell activating factors has shown some extremely promising results[(2)] as have trials of both Rontalizumab and Anifrolumab[(3)] (which block interferon-alpha).
Some key messages learnt from the running of the lupus trials include the importance of minimising the concomitant steroids and immunosuppression; ensuring the quality of those assessors participating in the clinical trials and the utility of employing an independent peer-review panel to monitor data as it is collected from the participating centres during the course of the trial. It is also evident that selecting patients who are more serologically active is likely to be of benefit both in clinical trials and in the clinic. However, we still need better biomarkers to help guide us; the identification of individuals expressing a high interferon alpha signature (and who thus might better benefit from an interferon alpha blocker) is one such example.
It remains ironic that Rituximab, the most widely used monoclonal antibody in SLE, failed its endpoint in two clinical trials. However, detailed analyses of data from those trials have shown some encouraging trends including falls in dsDNA antibodies and improvement in some clinical parameters.
References:
[1] Dooley MA et al. N Engl J Med 2011; 365; 188.
[2] Isenberg et al. Ann Rheum Dis 2015; 74; 2006–18.
[3] Furie R et al. Arthritis Rheum 2015; 67 (suppl 10) (abstract).
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.7196

SP0153 LESSONS FROM APS TRIALS

M. Khamashta[1,2]. *[1]Rheumatology Dept, Dubai Hospital, Dubai, United Arab Emirates; [2]Lupus Research Unit, St Thomas Hospital, London, United Kingdom*

Prevention of thrombosis in patients with APS remains a vexing clinical problem. In patients with a history of thrombosis, there is considerable risk of recurrence, and long-term anticoagulation treatment with warfarin is effective in most cases. Existing evidence suggest that the use of DOACs for secondary thromboprophylaxis for APS patients with previous VTE is promising. Until new data from ongoing clinical trials are available, there is not enough evidence to consider using DOACs in patients with APS and previous arterial events. The efficacy of heparin and low-dose aspirin in APS patients with previous pregnancy losses is supported by 3 meta-analysis available on the topic. In patients with antiphospholipid antibodies but without a previous thrombotic event, most physicians in the field recommend thromboprophylaxis with low-dose aspirin. Given the diversity of clinical presentations and medical specialties involved, it is not surprising that treatment of APS has been subject of intense debate. Due to the difficulty in conducting trials in the setting of a relatively rare condition, well designed multicenter studies (such as registries) using actual classification criteria and standardized tests should be performed in the future to answer all the opened questions regarding management of APS.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.7284

SATURDAY, 17 JUNE 2017

Genomic imprinting and post-translational modifications

SP0154 RATIONALE TO TARGET IMMUNE MEMORY RESIDING IN INFLAMED TISSUES

H.-D. Chang. *German Rheumatism Research Center Berlin, Berlin, Germany*

T helper (Th) lymphocytes play a major role in the regulation of immune responses and are thought to initiate and drive chronic rheumatic inflammation. Memory Th lymphocytes persist in the inflamed tissue and are refractory to therapeutic intervention. In chronic inflammation Th lymphocytes have undergone molecular adaptations, such as the upregulation of Twist1 and the microRNA miR-148a, which are not found in circulating Th lymphocytes, and support the survival of the Th cells within the inflamed tissue. Within the inflamed tissue, the Th lymphocytes constantly recruit and activate inflammatory cells, such as monocytes/macrophages and granulocytes through the secretion of particular chemokines and interleukins. The monocytes/macrophages in turn can recruit more Th cells into the inflamed tissue. Disrupting this vicious circle by specifically targeting the memory Th cells resident in the inflamed tissue by interfering with their molecular adaptations could be an interesting therapeutic option.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.7278

SP0155 THE ROLE OF POST-TRANSLATIONAL MODIFICATION AND AUTOREACTIVITY

R. Toes. *Rheumatology, Leiden University Medical Center, -Leiden, Netherlands*

Rheumatoid arthritis (RA) is a prototype autoimmune disease, with the hallmark signs of synovial inflammation and the presence of autoantibodies. Of the different autoantibody systems present in RA, rheumatoid factors (RF) are probably the best studied. Their presence was first detected >70 years and it was in the late 1950s when it was realized that RF reacted to gamma globulins. Since the discovery of RF several other autoantibody systems have been discovered in RA, many of them directed against post-translationally modified protein antigens. The most prominent example of such autoantibodies are anti-citrullinated protein antibodies (ACPA), which are directed against a wide-array of citrullinated proteins. Now RF and ACPA determination are the two major diagnostic laboratory tests for RA and part of the EULAR and ACR criteria for RA.
In the past few years, it has become clear that the autoantibody response present in RA extends towards several other modified proteins, such as proteins modified by acetylation or carbamylation. As all these auto-antibodies recognize Post-Translationally Modified (PTM) proteins, these antibodies are collectively called Anti-Modified Protein Antibodies (AMPA). In the context of this presentation, I will focus on the auto-antibody response against citrullinated, carbamylated and acetylated proteins.
Carbamylation leads to the formation of homocitrulline. Structurally, homocitrulline greatly resembles citrulline but is one methylene group longer. Citrulline is generated when PAD enzymes modify the amino acid arginine. In contrast, the amino acid homocitrulline is generated by a chemical reaction in which cyanate reacts with the amino acid lysine. Arginine and lysine are located at different positions in the amino acid sequence of proteins, and therefore these modifications occur at different positions in proteins with different flanking amino acids. Intriguingly, although homocitrulline residues can also be recognised by auto-antibodies, these auto-antibodies often do not crossreact with citrulline. Acetylation is a process where acetyl groups are added to free amines of lysine residues by acetyl transferases. Acetylated lysine does not resemble citrulline but bears similarity to homocitrulline except at the side chain terminal amine, which is replaced by a methyl moiety.
By now it is clear that AMPA consist of different auto-antibody families that are largely distinct, but that can also display a certain degree of cross-reactivity. Therefore, the notion is emerging that, although cross-reactivity exist, different classes of AMPAs are generally seen as distinct auto-antibody families that target different antigens, but intriguingly often co-occur. As the AMPA-responses in RA are often found together, it indicates that –somehow- AMPA-reactivity has a commonality that is currently not understood.
Although, the reason why an immune response starts against PTM proteins is not known, it appears crucial to obtain understanding on the breach of tolerance towards PTM proteins as the immune response against these proteins has been intimately implicated in disease-pathogenesis. Understanding the full AMPA response, the triggers that drive AMPA production, their mutual crosstalk and the pathways by which AMPA and/or AMPA-expressing B cells possibly contribute to RA will be important for the development of curative interventions in RA. In the context of this presentation, some of these aspects will be discussed.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.7219