

Epidemiologic studies have shown that not only fracture risk, but also mortality is increased after fracture, and that adequate therapy can not only decrease fracture risk but also increase survival.

Fracture risk is not constant over time. It is highest the years following a fracture, and immediately increases in some instances, such as after starting glucocorticoids or androgen deprivation therapy. This has raised the concept of "imminent" fracture risk, in contrast to long-term fracture risk as included in FRAX. In this context, we present the the EULAR initiative, in collaboration with EFORT, that published recommendations for multidisciplinary acute fracture care, including orthogeriatric care after hip fracture, and subsequent fracture prevention at the Fracture Liaison Service.

The presence, number and severity of vertebral fractures contribute to fracture risk, independent of BMD. Most vertebral fractures are subclinical and can therefore only be diagnosed by imaging of the spine. The role of vertebral fracture assessment (VFA) using DXA will be discussed.

New treatment insights will be reviewed, including for glucocorticoid users, combined and sequential treatments with anti-resorptive and bone forming drugs, real world data and the role of fall prevention.

Prescription of and adherence to treatment are still major issues. In patients adherent to therapy, new insights and recommendations will be reviewed on the need for early treatment, duration of treatment and the clinical approach when considering stopping drug therapy.

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What is behind vasculitis?

SP0131 AUTOIMMUNE ATHEROSCLEROSIS

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Arthritides have been associated with accelerated atherosclerosis to increased vascular disease risk. Traditional risk factors, as well as the role of systemic inflammation including cytokines, chemokines, proteases, autoantibodies, adhesion receptors and others have been implicated in the development of these vascular diseases. Accelerated atherosclerosis and increased cardio- and cerebrovascular morbidity and mortality have been observed in rheumatoid arthritis (RA) and spondyloarthropathies (SpA).

Endothelial dysfunction, overt atherosclerosis and vascular stiffness may be indicated by brachial artery flow-mediated vasodilation (FMD), common carotid intima-media thickness (ccIMT) and aortic pulse-wave velocity (PWV), respectively. These abnormalities have been described in most inflammatory rheumatic diseases. While ccIMT and stiffness are relatively stable, FMD may be influenced by many confounding factors.

In addition to traditional vasculoprotection, immunosuppressive agents including corticosteroids, traditional and biologic DMARDs may have significant vascular and metabolic effects. The official EULAR recommendations on the assessment and management of cardiovascular disease in arthritides have been published.

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SP0132 VIRUSES DRIVING VASCULITIS

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Viruses have long been associated with varying forms of vasculitis in both pre-clinical models and human diseases. Immunopathogenic mechanisms have varied and include direct vascular invasion, immune complex mediated and more recently novel mechanisms which include autoinflammatory like responses. This discussion will review major advances in the field of medical virology as it applies to rheumatic diseases, especially vascular inflammatory disease, including an introduction to the human and more specifically vascular microviromes. Major forms of virally mediated vasculitis will be discussed with an emphasis on new viral vasculitis syndromes largely defined by next generation sequencing and their potential clinical impact.

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SP0133 ANCA AND THEIR ENVIRONMENT

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The association between antibodies to neutrophil cytoplasm (ANCA) and systemic vasculitis has transformed our understanding of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). ANCA undoubtedly play a major role in their pathogenesis. There are different forms of ANCA, but only two of direct clinical relevance: cytoplasmic c-ANCA (usually directed against proteinase 3, PR3), and perinuclear p-ANCA (usually directed against myeloperoxidase, MPO). P-ANCA can also

be directed against other antigens including bactericidal/permeability-increasing protein, lactoferrin, human neutrophil elastase, cathepsin G and azurocidin, but their clinical significance is not clear.

Transfer of MPO ANCA in humans (maternal-foetal route) and animal models (necrotizing pauci-immune glomerulonephritis after passive transfer of purified antibody or splenocytes from MPO-deficient mice immunized with murine MPO) has resulted in features of MPA. By contrast, the pathogenicity of anti-PR3 antibodies is less well-established. There is a significant genetic predisposition to disease in patients with AAV. Patients with PR3-ANCA have a strong association with HLA-DP and genes encoding alpha-1-antitrypsin and proteinase 3; by contrast, patients with MPO-ANCA have an association with HLA-DQ. Other factors that could interact with ANCA include: loss of B cell and T cell tolerance; direct involvement by neutrophils and their mediators in vascular injury and damage, degranulation and cytokine production; environmental exposure to silica or certain strains of *Staphylococcus aureus*, coupled with a lack of effective T cell regulation to prevent inflammation. Neutrophils spontaneously release of neutrophil extracellular traps (NETS), which directly cause endothelial cell damage and complement activation. NETS retain proteinase 3 and myeloperoxidase, helping to break immune tolerance and inducing antibody formation. The alternative complement pathway plays a crucial role in the pathogenesis of AAV. Activated neutrophils produce C5a, which in addition to recruitment, primes additional neutrophils for further activation by ANCA. C3a, C5a, soluble C5b-9 are elevated in active disease and plasma levels of complement factor H, a regulator of the alternative complement pathway is significantly lower in patients with active AAV.

Central to the pathogenesis of AAV is a dysregulated immune response to ANCA and aberrant expression of their target autoantigens, MPO and PR3. Environmental exposure to silica may inactivate α 1-antitrypsin, whilst activating monocytes and macrophages releasing cytokines such as interleukin-1 and TNF- α , oxygen radicals and lysosomal enzymes (such as PR3 and MPO). Other environmental interactions include CpG-ODN, a short synthetic DNA containing unmethylated CpG and several drugs, especially propylthiouracil and levamisole-adulterated cocaine. Some of these associations could provide a better insight into the development of ANCA associated disease.

ANCA play a central role in the pathogenesis of systemic vasculitis, supported by a dysregulated immune system, with significant interactions with micro-organisms, environmental toxins and drugs, all of which can contribute to the development and severity of disease.

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Cytokine taxonomy: reflection in the therapy of arthritides and other IMIDs

SP0134 INTERLEUKIN-2 THERAPY IN SLE

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There is an unmet need for more effective and selective therapeutics in severe autoimmune diseases such as systemic lupus erythematosus (SLE). A deeper understanding of the pathogenic mechanisms in the past has led to the clinical translation of low-dose interleukin-2 (IL-2) therapy which primarily aims to restore the activity of regulatory T cells. First results from phase I/II studies are promising by proving the selective expansion of regulatory T cells *in vivo* and by providing first evidence for the clinical efficacy of low-dose IL-2 therapy in SLE. Here we will summarize key findings which led to the development of this novel therapeutic concept and will highlight the main rationales for the clinical translation of low-dose IL-2 therapy in SLE.

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Regulatory molecules in connective tissue

SP0135 MYOSTATIN, SCLEROSTIN, SYNDECAN AND MORE

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Rheumatoid arthritis (RA) is the prototype of an inflammatory arthritis that is characterized by chronic inflammation, progressive cartilage destruction and bone erosion. Development of RA is marked by the hyperplasia of the synovial membrane as caused by an infiltration and accumulation of inflammatory cells such as macrophages and lymphocytes as well as an increase in the number of resident mesenchymal cells. These fibroblast-like synoviocytes (FLS) are a key part of the local immune system in the joints and integrate signals

form different sources into a pathological tissue response. Resorption of the juxtaarticular bone is part of this pathological tissue response and is denoted as focal bone erosion which occurs early in this disease and over time is associated with significant morbidity. Focal bone erosions are observed at the interface of pannus and bone tissue both marginally, where pannus invades cortical bone, and in the immediate subchondral bone, where the pannus invades the marrow space. Many of the cytokines and growth factors implicated in the inflammatory processes are secreted by FLS and have also been demonstrated to impact directly or indirectly on osteoblast and/or osteoclast differentiation and function. However, research of the last years has also identified some novel pathways by which i) osteoclast-mediated bone resorption is regulated and fine-tuned under inflammatory conditions such as in RA and that ii) link inflammatory bone resorption to other features of systemic autoimmunity such as the activation of developmental pathways or muscle weakness. This lecture will review some of these novel mediators and pathways, including members of the Wnt- signalling pathway (e.g. sclerostin), members of the GDF- family of growth differentiation factors (e.g. myostatin) and cells surface anchored proteoglycans (e.g., syndecans). Focusing on the role of these molecules in the FLS-mediated regulation of osteoclastic bone resorption, the lecture will point to general principles of inflammatory bone remodelling and discuss potential therapeutic implications for RA.

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SP0136 MULTIFACTORIAL TISSUE GROWTH FACTORS

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Connective tissue is a critical component of all organs and has special importance in the musculoskeletal system. In specialist tissues, such as bone, cartilage of muscle an in vascular structures and internal organs there is a mixture of less specialized connective tissue together with the specific tissue and organ specific cellular components. In addition to physiological function there are two other areas in which it plays a central role. Normal embryonic and postnatal growth and development, and tissue repair in response to injury. It has emerged that there are shared pathways, mediators and mechanisms in these different processes and that multifactorial tissue growth factors have an important role. In this way, these proteins can have a profound influence on multiple cell types and provide a mechanistic link in many complex chronic diseases. It is notable that pathways that are perturbed in one chronic disease, such as atherosclerosis or osteoarthritis may be similarly disrupted in different context in conditions such as lung fibrosis or scleroderma. Transforming growth factor beta family members are prototypic examples of this class of protein. This included TGFbeta isoforms but also the related bone morphogenetic (BMP) and activin family of proteins. They share chemical structure and an ability to regulate multiple cell types in a context specific way. In addition, there is remarkable complexity in their regulation with intrinsic inhibitory mechanisms to protect from inappropriate biological activity. Their role in repair means that activation of preformed protein may regulate biological effects. Proteins regulated by the TGFbeta family, such as the CCN family of matricellular proteins and some of the cardinal growth factors and cytokines share properties. There is functional and signaling redundancy and cross talk. Conceptually it is interesting to envisage dysfunctional networks of cytokines in disease that may be attenuated by extracellular blocking or antagonism. Insights for many areas of developmental biology and pathology have informed about this challenging area of molecular medicine.

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SP0137 FROM GLYCOSYLATION TO INFLAMMATION

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One of the best studied posttranslational modification of immunoglobulin G (IgG) is the addition of a complex glycan to asparagine 297, which is required for IgG to bind to Fc-receptors and for the activation of complement via the classical activation pathway. In the absence of the glycan the IgG usually behave like a lame duck unable to execute its effector functions. The sugar tree is polymorphic and there are several functional consequences related to the glycan. The terminal sialylation, the presence of galactose, the core fucosylation and the insertion of a bisecting third sugar chain all reportedly modify the biological and functional activities of IgG.

As examples for the impact of Asp-297 associated glycans to the activity I will present (I) the sialylation of anti-histone autoantibodies in patients with systemic lupus erythematosus (II) the exposure of sugar epitopes by random IgG isolated from patients with rheumatoid arthritis (III) the molecular analysis of the glycan of random IgG isolated from patients with inflammatory diseases and controls and (IV) and finally the glycosylation of IgG-anti-phospholipid autoantibodies in healthy children.

(I) The autoantibodies are mainly found in the non-sialylated fraction of the anti-histone autoantibodies which can be considered inflammatory IgG.

(II) The circulating random IgG from patients with rheumatoid arthritis show an

increased exposure of the Asp-297 associated glycans.

(III) The molecular analysis of the glycan of random IgG isolated from patients with systemic lupus erythematosus, rheumatoid arthritis, sepsis showed disease-specific glycans.

(IV) The non-pathogenic IgG-anti-phospholipid autoantibodies isolated from healthy children displayed an increased sialylation when compared to the pathogenic autoantibodies from adults with anti-phospholipid syndrome.

The examples point to a strong impact of IgG glycosylation in the etiopathogenesis of chronic inflammatory rheumatic diseases. One should consider to include IgG glycan analyses into the diagnostic repertoire for autoantibodies.

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Patient engagement in research: best practices, benefits, and challenges

SP0138 THE CHALLENGES OF PATIENT INVOLVEMENT IN SCIENTIFIC RESEARCH. HOW TO ACHIEVE TRUE REPRESENTATION OF THE PATIENTS' VOICE?

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There is a strong call in the western world for collaborative research. Rheumatology is one of the disciplines that has explored best practices and paved the way to implement lessons learned. Although good methodologies for evaluating the impact of patient participation stay behind, we have been able to develop expert-based recommendations for collaboration. They are helpful for both researchers and patient representatives, but they do not address all concerns that occur in daily practice. In this lecture current challenges of integrating the perspectives of patients in clinical research will be discussed: 1. Defining the role and complementary value of patient research partners; How can patients in the role of collaborative partner contribute to research in addition to the data that patients provide as respondent or study participant? 2. Facilitating and guiding researchers in collaborative research; We have experience in preparing and educating patient representatives for their role in research, but how should researchers be trained and supported? 3. Preserving the patients' voice throughout the research process; Qualitative research may elicit patients' experiences with health care or health interventions, but what is needed to guarantee that these findings are not lost in the rigorous process of producing scientific knowledge? 4. Demonstrating impact of collaborative research to funders and the public; Despite many case studies reporting a great variety of patient participation methods, there are no clinical trials nor consensus on a validated methodology for assessing the outcomes of patient involvement in research.

For each challenge we will try to propose a way forward. These challenges will also be discussed at the newly established EULAR working group for collaborative research.

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SP0139 MEANINGFUL PATIENT AND PUBLIC INVOLVEMENT IN PLANNING RESEARCH

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Historically, services providing care for people with long term conditions (LTCs), together with any associated research agendas, have been driven entirely by clinicians. In many cases this is well meaning and is done with some consideration of what patients need, but almost always the end result relies on the clinicians' interpretation of what they think patients need.

Recently it has become more usual to involve patients in planning research projects and service changes directly. Initial attempts to give patients genuine input were *ad hoc* in nature and so patient contributions could be lacking, ignored or misinterpreted.

In many cases having poor patient input is worse than no input at all as it lends false credibility to the process. Lately a range of formal requirements, arrangements and methods have become adopted and this presentation will focus on how these can be brought to bear to ensure meaningful patient and public involvement in planning research. From national guidance such as the UK's INVOLVE initiative, to local standard operating procedures we will share experiences and lessons learned.

The session will close with a practical summary of how to make PPI contributions genuine and meaningful, and some insights into possible future developments as this aspect of the research process matures and consolidates.

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