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MEETING ABSTRACTS Open Access

Proceedings of Osteorheumatology 2011: International Congress on Bone Involvement in Arthritis

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INTRODUCTION

A1

Osteo-Rheumatology: a new discipline?

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The "Bone Involvement in Arthritis" International Meeting was first held in Venice, in 2004, with the objective of bringing together distinguished international experts in the fields of bone metabolism and rheumatic diseases to discuss emerging knowledge regarding the interplay between rheumatic diseases and the bone tissue. The growing interest and the continuous progresses on the topic led to the organization of six other meetings, which included several different established clinicians and/or researchers.

Since its origin, the meeting focused on the interactions between the bone tissue, the immune system and the cartilage in osteoarthritis, rheumatoid arthritis and spondyloarthropathies, always considering the two sides of the coin: the basic and clinical. In past years, as well as this year, specific sessions were dedicated to osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis, respectively, with a starting session considering the general aspects of the topic. In this context, the bone damage as an early manifestation of arthritides, the systemic skeletal involvement in RA, the crucial role played by subchondral bone in the pathogenesis and progression of OA, the pathophysiology of glucocorticoids damage on the bone tissue, and the potential beneficial effects of newly approved agents such as bisphosphonates and biologics, but not only, were discussed.

In 2011, the meeting has been named, for its first time, "Osteo-Rheumatology", thus implying the necessity of giving a more clear definition to topics presented and the issues raised. Even this year, experts in bone and rheumatic diseases interacted to improve our knowledge regarding the bone involvement in arthritis and to raise issues to be addressed in the future.

MEETING ABSTRACTS

A2

Long-term osteoporosis treatment: myth or reality?

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Arthritis Research & Therapy 2012, **14(Suppl 2):**A2

Several pharmacological agents [bisphosphonates (BPs), SERMs, teriparatide, PTH 1-84, strontium ranelate, denosumab] have been approved worldwide for the prevention of fragility fractures in patients at risk. In pivotal randomized-controlled trials (RCTs), these drugs demonstrated to reduce the incidence of new vertebral fractures, and, in some cases, of new non-vertebral and hip fractures, in women and men with primary and glucocorticoid-induced osteoporosis, with a good profile of safety and tolerability. Most of the studies, however, were designed to assess the efficacy and safety of these drugs for 3 to 5 years, and only few of them extended over 5 years (BPs).

Although RCTs extension studies were carried out in smaller samples compared to the original baseline populations enrolled, their results support the sustained beneficial effects on skeletal metabolism of alendronate (10 years), zoledronate (6 years) and risedronate (7 years) on the long term. Due to their pharmacological properties, BPs have also demonstrated to prolong their efficacy after discontinuation in specific subgroups of patients.

In recent years, some concerns have been raised about long-term safety of BPs, due to "unexpected" rare adverse events (AEs) potentially associated with their use (atypical fractures, ONJ and esophageal cancer). Indeed, a cause-effect relationship has not been yet demonstrated. However, given the dramatic implications of these rare AEs, a drug-free holiday should be considered in patients treated for more than 5 years with BPs, after an accurate evaluation of risks and benefits.

Regarding the recently approved anti-osteoporotic agents less information are available. Denosumab have been shown to produce a sustained increase of bone mineral density over 8 years of treatment, and

to reduce the risk of new fragility fracture up to 5 years of continuous treatment. Similar results have been described also for strontium ranelate. In this context, studies are warranted to clarify when and for how long a drug-free holiday should be considered in patients receiving BPs. Moreover further trials are needed to clarify the long-term safety and beneficial effects of the newly approved agents (denosumab, strontium ranelate).

A3

Clinical significance of bone changes in osteoarthritis

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Knee OA is thought to be a largely mechanically-driven disease. Pertinent to this, bone is a dynamic tissue that adapts to loads by remodeling to meet its mechanical demands (Wolff's Law) [1,2]. As such, it is not surprising that bone changes, such as increased tibial plateau area and bone turnover, occur early in OA [3,4]. Recently, MRI-based 3D bone shape has been shown to track concurrently with OA onset, and to predict incidence of radiographic knee OA 12 months before its onset [5]. Further, in radiographically normal tibiofemoral knee joints, subchondral bone changes, such as bone marrow lesions (BMLs) on MRIs, are common.

Although MRIs allow direct visualization and morphologic evaluation of joint tissues not otherwise discernible on x-ray, their specific pathologies need to be examined by direct evaluation to gain further pathophysiologic insight. BMLs adjacent to the subchondral plate have been shown to have increased bone volume fraction and increased trabecular thickness, but reduced tissue mineral density (i.e., hypomineralized) [6], consistent with OA being associated with increased bone turnover. BMLs may render these areas mechanically compromised and susceptible to attrition. Indeed, BMLs are strongly associated with occurrence of subchondral bone attrition (SBA) [7]. Both subchondral bone abnormalities are associated with cartilage loss as well [8,9]. In keeping with knee OA being mechanically-driven, meniscal pathology, often the result of injury, is associated with new and enlarging BMLs [10]. Further, malalignment is associated with both BMLs and SBA [11,12].

The contributions of these structural abnormalities to the clinical manifestations of knee OA are becoming better understood. While it is widely thought that there is a structure-symptom discordance in knee OA, such observations do not take into account all of the potential factors that can contribute to between-person differences in the pain experience [13]. Recent work that used novel methodology to overcome this problem has demonstrated that pain fluctuation is associated with changes in BMLs, as well as synovitis and effusion [14]. SBA has also been associated with knee pain [15], but the relationship of osteophytes to pain has been conflicting. A challenge that remains in studying the specific contribution of pathologic features of OA to pain is the co-existence of multiple MRI abnormalities, making it difficult to identify individual pathologic features' effects.

Understanding the pathophysiologic sequences and consequences of OA pathology will guide rational therapeutic targeting. Importantly, rational treatment targets also require understanding what particular structures contribute to pain as pain is the reason patients seek medical care.

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A4

IL-1 inhibition in autoinflammatory diseases

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Inherited autoinflammatory syndromes (IAS) are a group of recently identified monogenic diseases characterized by recurrent episodes of systemic inflammation.

Muckle-Wells Syndrome, Familial Cold Autoinflammatory Syndrome and Chronic Infantile Neurological Cutaneous and Articular Syndrome are IAS due to mutations in a single gene, CIAS1 (cold-induced autoinflammatory syndrome 1, or NALP-3), encoding a protein called cryopyrin which is an essential component of an intracellular multiprotein complex named inflammasome, that play a crucial role in the production and secretion of interleukin (IL)-1 These diseases are characterized by excessive production of IL-1 and have a dramatic response to IL-1 inhibition.

More recently, IL-1 inhibition has also been shown to be effective in another AID (TNF-receptor associated periodic syndrome or TRAPS) as well as in other conditions such as systemic juvenile idiopathic arthritis and recurrent idiopathic pericarditis. This has suggested that also these two last diseases may represent autoinflammatory conditions.

A5

Chondrogenesis, joint formation, and cartilage metabolism

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Chondrogenesis occurs as a result of mesenchymal cell condensation and chondroprogenitor cell differentiation. The chondrocytes then form the cartilage at the end of the opposing bones with the intervening interzones formed during cavitation or they undergo proliferation, terminal differentiation to chondrocyte hypertrophy, and apoptosis in a process termed endochondral ossification, whereby the hypertrophic cartilage is replaced by bone. A similar sequence of events occurs in the postnatal growth plate and leads to rapid growth of the skeleton. Human adult articular cartilage is a complex tissue of matrix proteins that varies from superficial to deep layers and from loaded to unloaded zones. A major challenge to efforts to repair cartilage by stem cell-based and other tissue engineering strategies is the inability of the resident chondrocytes to lay down new matrix with the same properties as it had when it was formed during development. This is particularly true of the collagen network, which is susceptible to cleavage once the proteoglycans are depleted. Thus, understanding and comparing the mechanisms of cartilage remodeling during development, osteoarthritis (OA), and aging may lead to more effective strategies for preventing cartilage damage and promoting repair. To identify and characterize mediators of cartilage remodeling common to these processes, we are using culture models of primary human and mouse chondrocytes and cell lines and mouse models to manipulate and compare gene expression with complementary approaches. MMP-13, the major type II collagen-degrading collagenase, is regulated by both stress and inflammatory signals that not only contribute to irreversible joint damage (progression) in OA, but importantly, also to the initiation/onset phase, wherein chondrocytes in articular cartilage leave their natural growth - and differentiation-arrested state. We and other investigators have found that there are common mediators of these processes in human OA cartilage and from early through late stages of OA in mouse models, including the surgical models (good matrix with abnormal loading) and the genetic models during aging (bad matrix with normal loading). We are validating our in vitro analyses of the signaling and transcriptional mechanisms that determine the expression and activities of these mediators by in vivo analyses of the consequences of knockout or transgenic overexpression of these genes in mouse models. In current studies, we are examining the epigenetic mechanisms and using proteomics and genomics approaches to map the signaling networks and microRNA targets that impact on gene expression programs during the onset and progression of OA in both human and murine cartilage. Since the chondrocytes in adult human cartilage are normally quiescent and maintain the matrix in a low turnover stated, understanding how they undergo phenotypic modulation and promote matrix destruction and abnormal repair in OA may to lead to identification of critical targets for therapy to block cartilage damage and promote effective cartilage repair.

A6

Subchondral bone remodelling and osteoarthritis

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Osteoarthritis (OA) emerges of the inharmonious functioning of joint tissues, particularly subchondral bone (SB) and articular cartilage that are two mechanically and biologically intertwined tissues [1]. Thus, biomechanical, biochemical and/or genetic alterations affecting any joint tissue may cause anomalous intra-articular stresses and subsequent tissue damage associated to a failure of repair [2]. Specific anatomical regions have been described in the bone underlying joint cartilage, including the subchondral cortical plate, subchondral trabecular bone and sub-articular bone [3]. Each region likely contributes differently to cartilage pathology. However, a lack of clear boundaries between these tissues by current imaging techniques generates some confusion in their study and thorough research will help to improve our understanding of SB properties. In addition, bone at the joint margins is markedly active since is the site of osteophyte development in OA. The close relationship between SB and joint cartilage evokes an unanswered question with valuable therapeutic implications [4]. In this context, the relationship among SB microstructure and remodeling, and cartilage destruction becomes important.

Yet, it remains controversial whether SB alterations precede the cartilage damage or they further appear during the evolution of the disease. In fact, SB remodeling abnormalities, especially increased bone turnover, have been detected early in the evolution of some forms of OA in animal models [5,6] and humans [7,8]. On the other hand, OA and systemic osteoporosis (OP) share a paradoxical relationship, being probable that high as well as low bone mass conditions result in induction and/or OA progression [4]. Interestingly, improving SB integrity showed to reduce the progression of cartilage damage in an animal model of OA preceded by OP [9]. Therefore, both bone mass phenotypes may be considered risk factors for OA initiation. The presence of other risk factors such as skeletal shape abnormalities, joint overload or obesity may have a synergistic effect for OA initiation. In addition, inflammatory mediators released by the articular cartilage may lead to SB loss by increasing bone remodeling in OA. Accordingly, OA treatment goals must consider the improvement of SB integrity. This therapeutic approach should be individualized depending on the patient BMD status and OA phenotype, and subsequently the use of drugs should also be individualized for each patient [10]. Recent findings suggest that the same drugs could be useful for treating simultaneously both processes, at least in a subgroup of patients with OA and concomitant OP.

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A7

Cross-talk between subchondral bone and articular cartilage in osteoarthritis

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The interest in the relationship between articular cartilage and the structural and functional properties of peri-articular bone relates to the intimate contact that exists between these tissues in diarthrodial joints. Much of the interest and continuing controversy regarding the relationship between these tissues dates back to the original suggestion by Radin and Rose that alterations in the mechanical properties of subchondral bone could adversely affect the functional state of chondrocytes and the integrity of the overlying cartilage. They hypothesized that the

deterioration in articular cartilage associated with the osteoarthritic process was secondary to an initial increase in subchondral bone stiffness induced by repetitive mechanical loading. Numerous approaches have been used to establish that the changes in periarticular bone occur very early in the development of OA. Although chondrocytes also have the capacity to modulate their functional state in response to loading, the capacity of these cells to repair and modify their surrounding extracellular matrix is relatively limited in comparison to the adjacent subchondral bone. This differential adaptive capacity likely underlies the more rapid appearance of detectable skeletal changes in OA in comparison to the articular cartilage. Given the intimate mechanical and biological interaction between the articular cartilage and subchondral bone it is likely that alterations in the composition and/or structural organization of either tissue will modulate the properties and function of the other joint component. An additional factor that affects the interaction between these tissues is the gradual expansion of the zone of calcified cartilage and advancement of the tidemark that occurs with aging and progression of OA and contributes to overall thinning of the articular cartilage. The precise mechanisms involved in this process have not been definitively established and could include the release of pro-angiogenic factors from chondrocytes in the deep zones of the articular cartilage that have undergone hypertrophy and/or the influences of microcracks that have initiated focal remodeling in the calcified cartilage in an attempt to repair the microdamage. In addition, this process markedly increases the mechanical stresses in the deep zones of the cartilage matrix, which likely contributes to the acceleration in OA cartilage deterioration. In summary, there is the need for further studies to define the pathophysiological mechanisms involved in the interaction between subchondral bone and articular cartilage and for applying this information to the development of therapeutic interventions to improve the outcomes in patients with OA.

A8

The model of erosive hand osteoarthritis

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Arthritis Research & Therapy 2012, **14(Suppl 2):**A8

Hand osteoarthritis (OA) is not one disorder, but a heterogeneous group of disorders. Erosive HO (EOA) is a radiographic subset of hand OA and defined on the basis of radiographic central erosions and collapse of the subchondral bone plate. At the moment it is unknown whether EOA comprises a separate disease entity with specific risk factors and pathogenesis or a more severe stage of hand OA.

EOA is a rather uncommon subset of OA. In the general population a prevalence of EOA in the interphalangeal joints (IPJs) of approximately 3% was estimated in adults aged 55 years and over. In the population with hand pain or with symptomatic hand OA the prevalence estimates were around 7% and 10%, respectively. However in a population with symptomatic hand OA from secondary care, the prevalence of EOA raised to 25%.

The presence or absence of specific risk factors for EOA could learn whether EOA is a separate disease entity or a severe stage of hand OA. The first step in this research deals with heritable factors. Several studies suggest that EOA is heritable. Within patients with hand OA, several genetic factors are demonstrated to be associated with EOA when compared to non-erosive hand OA, but further replication of found results is needed.

EOA is a highly clinical relevant subset, since EOA leads to a higher clinical burden and worse outcome than non-erosive hand OA. Patients with EOA report more pain and functional limitations, worse hand mobility, less satisfaction with hand function and aesthetics than those with non-erosive hand OA. However patients with EOA have also more nodes, which were also found to be a determinant of clinical outcome. Taking in account nodes, only hand mobility and patient satisfaction remained different between the groups.

In the pathophysiology of EOA inflammation could be important. Already since 1972 it is noted that inflammation is involved in EOA, as also witnessed by histology of synovial biopsies of erosive DIPJs and PIPJs in an inflammatory stage, showing intense proliferative synovitis indistuinguishable from rheumatoid arthritis. Recently the presence and role of inflammation is further investigated by ultrasound and MRI studies. Moreover, ultrasound studies showed that not only in erosive but also in non-erosive joints in EOA more power Doppler signal and effusion is seen in comparison to joints in non-erosive hand OA, suggesting an underlying cause for erosive evolution.

Another important observation is that erosions are more frequently present in hand OA than based on radiography when using ultrasound. The meaning of erosions only detected on MRI and ultrasound has to be elucidated.

In conclusion, EOA is a highly clinical relevant subset of hand OA. Whether it is a separate disease entity is at the moment unknown, but needs further study. Inflammation seems of importance, already in the pre-erosive stages. Further research in this hand OA subset could lead to new treatments for patients with EOA.

A9

Damage progression in rheumatoid arthritis: the role of biologic agents

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Given the strict link between structural damage and disability, the prevention of disease progression can be considered the ultimate goal of every rheumatoid arthritis (RA) treatment strategy. At least 4 imaging tools for measuring damage progression in RA are now available: x-rays, ultrasounds, MRI, and CT scan. However, so far in main randomized clinical trials (RCTs) radiography was used as the gold standard for structural damage assessment. Several different radiographic scoring methods have been proposed, but nowadays the most widely used are the Sharp method and its subsequent modifications proposed by van der Heijde and Genant. A recently published paper has demonstrated a strong correlation between various scoring systems. Sixteen main registrative RCTs evaluating the performance of biologic agents in slowing RA structural damage can be found in the literature. Overall, all biotherapies demonstrated a significantly lower damage progression than methotrexate (MTX) used both in monotherapy (adalimumab in the PREMIER and etanercept in the TEMPO trials) and in combination with MTX, with the exception of golimumab in the GO-FORWARD trial. So far, no RCTs head-to-head comparing various biologic agents have been yet performed, and indirect comparisons may have several important limitations regarding study design, study population selection, and choice of used radiographic scoring method. Standardization of scores generated with different scoring systems, matching clinical trials by disease duration and previous treatments, and evaluating the annual estimated progression in each trial may be crucial key factors in order to better compare data coming from different RCTs. Applying this comparison approach, the impact of various biologic drugs in slowing x-ray progression seems to be similar in early RA. On the contrary, the differences in study population characteristics are too marked in late RA for an adequate comparison of biologics performance in this clinical condition. Anyway, the overall impact of biotherapies versus MTX on damage progression seems to be similar in early and in late RA patients. The results in the open extension phase of some previously mentioned RTCs seem to confirm the positive effect of biologic drugs on structural damage in long-term evaluation. A few data coming from RCTs (TEMPO trial) suggest the possibility of repairing bone erosions in patients treated with TNF blockers. Preliminary data on denosumab suggest a possible role of this RANK-L inhibitor in the treatment of RA, mainly as a part of a combination therapy in association with synthetic DMARDs.

A10

Viscosupplementation in the treatment of osteoarthritis

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Osteoarthritis is the most common joint disease and a major cause of disability. The changes in the lubricating properties of synovial fluid lead to

significant pain and function loss. The injection of hyaluronic acid (HA) into the joints, called Viscosupplementation, improves the biochemical properties of synovial fluid (SF) in osteoarthritis (OA) joints. The clinical effect is pain relief and someone has hypothesized a disease modifying activity . Intra-articular (IA) hyaluronan therapy has been used in the treatment of symptoms associated with OA of the knee and other joints with a very favourable safety profile. The high concentration of HA in SF is essential for normal joint function. Balazs and Denlinger were the first to suggest that the favourable effects of IA HA therapy in OA was related to the SF rheological properties restoration. Many subsequent studies have supported that IA HA therapy could be a symptom-modifying approach. The hypothesis that HA could bind specific receptors is now widely accepted. The cluster determinant 44 (CD44), the intracellular adhesion molecule-1 (ICAM-1) and hyaluronate-mediated motility receptor (RHAMM) expressed in many cells, are some of those implicated in the process. The binding of HA with its specific receptors has been reported to trigger various intracellular signals such as cytokine release and stimulation of cell cycle proteins. The consequences of these interactions is to stimulate cell functional activities such as cell migration and proliferation. Presently, there are several different HA products with different molecular weight available for injection. Several meta-analysis have reviewed clinical trials published in the last years using different HA preparation that support the benefit and safety of repeated treatment with IA HA. Many trials indicate that sodium hyaluronate is well tolerated and as effective after multiple courses of treatment as it is after a single course. Other informations state that viscosupplementation is an effective treatment for patients with knee OA who have ongoing pain or are unable to tolerate conservative treatment or joint replacement. Viscosupplementation appears to have a slower onset of action than intra-articular steroids, but the effect seems to last longer. Viscosupplementation is an effective treatment for OA of the knee with beneficial effects on pain, function and patient global assessment at different post injection periods but especially at the 5 to 13 week with a dramatic effect on the reduction of NSAIDs monthly consumption. In some analyses viscosupplements were comparable in efficacy to systemic forms of treatment, with more local reactions but fewer systemic adverse events. In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA. In one systematic review intra-articular hyaluronic acid has not been proven clinically effective and may be associated with minimal and transient risk of adverse events. The heterogeneity of these studies limits definitive conclusions on different treatment regimen with different molecular weight HA but, in our opinion, we think that generally HA products may determine a reduction of symptoms by 40%. Few data exists in literature about the viscosupplementation of hip OA, the second most common site of the disease after the knee. The intra-articular injection of the hip is not as easy as for the knee, mainly for anatomical features of the joint and the proximity of "sensitive" structures such as the femoral artery and nerves. Even though hip injection may be performed "blindly", nevertheless failure rate is significant and when using a slow absorbing viscosupplement like hyaluronan the potential local complications may jeopardize the therapeutic benefit. For such reasons, it has been suggested to perform intra-articular injection of the hip under radiological or ultrasound control. Although several ultrasound guidance techniques were available we developed a personal one using an antero-superior approach. The efficacy data, presents in literature, underline significant improvement in pain and function as has been shown in the knee OA despite the small size of the sample and the short period of observation have not allowed to point out a change in the natural history of the disease. In order to confirm these promising data large scale double blind controlled trials must be carried out. Despite recent progress, many unresolved issues require further study. These include the necessity to determine the relative economic efficacy of viscosupplementation, explore the therapeutic effectiveness and safety, clearly define the relation between molecular weight and clinical effectiveness of the different hyaluronan products, establish optimal dosing regiments and assess potential synergistic or additive effects with other modalities such NSAIDs and SYSADOA. If hyaluronan derivatives are eventually proven to have clear disease-modifying effects, it may then be reasonable to consider their use early in cartilage injury or disease, before the onset of syntomatic OA. Additional well-designed randomized controlled trials with high methodological quality are needed to resolve the continued uncertainty about the therapeutic effects of different types of hyaluronic acid products on osteoarthritis.

A11

Combination and sequential treatments in the management of osteoporosis

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Therapies of chronic diseases should be efficacious, convenient for the patient and devoid of side effects. In daily practice, the risk of serious outcomes and the preference of patients as well as the cost of the interventions should also be considered. The pathophysiological basis of osteoporosis provides the rationale for the use of interventions that either reduce bone resorption and turnover or stimulate bone formation. Several antiresorptive treatments are used in the treatment of osteoporosis but PTH is the only anabolic therapy currently available. Evidence for efficacy and safety from controlled studies has been obtained for up to 10 years for antiresorptives and up to 2 years for PTH. while short-term head-to-head studies with surrogate endpoints have also been performed. Such studies illustrate the different mechanism of action of the two types of interventions but do not allow any conclusions about any potential differences in antifracture efficacy. These considerations are reflected in recommendations of several regulatory authorities. It is also frequently assumed that antiresorptives should be given mainly to patients with high bone turnover while anabolics should be reserved for patients with low bone turnover. However, analyses of the results of trials with bisphosphonates and PTH 1-34 indicated that the antifracture efficacy of these agents is independent of prevalent rates of bone turnover. Further analysis of the pharmacodynamic responses to these treatments, reveal distinct patterns with attainment or not of steady-states that provide the basis for the design of regimens with the use of both types of therapies, in some patients at least. Most of the studies have been performed with bisphosphonates and PTH. Combination therapies, a common approach in the treatment of other chronic disease, do not confer any particular advantage compared to monotherapies, although the response may depend on the frequency of the administration of the bisphosphonate. In contrast, sequential therapies are very important for clinical practice and depend on the severity of the disease and the mechanism of action of the specific treatment. Such therapeutic approaches need to be explored further and their efficacy in reducing fracture risk, their safety as well as their cost-effectiveness need to be evaluated.

A12

Long-term efficacy and safety of biologics in rheumatoid arthritis

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Biologic agents have been used for more that twelve years in treating rheumatoid arthritis (RA) and other rheumatic diseases. Long-term analysis for both efficacy/effectiveness and safety is now feasible for the first anti-TNF agents available, namely infliximab, etanercept and adalimumab. Open-label extension studies have shown that clinical improvement is maintained up to10 years. However, these studies include only the patients who have sustained efficacy without the development of significant adverse events that would cause the patient to exit the study prior to closure. Therefore, as with any completer analysis of efficacy, the results reported are generally positive. Furthermore, clinical trial patients may not be representative of the entire patient population since in the clinic setting the indications for treatment with biologic agents are not identical to the inclusion criteria for trials. Only a minority of the patients in the clinical setting would have been eligible for the major trials; ineligible patients have lower baseline disease activity, more comorbidity, lower functional status and lower response rates. Despite these data, long term evaluation of effectiveness and safety in observational studies and registers has shown that TNF inhibitors are still a good choice in treatment

of RA and may be also associated with a reduced risk of cardiovascular events in patients with RA.

A13

The role of RANK ligand/OPG system in bone erosions in rheumatoid arthritis

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There is still growing insight on the links between the immune system and bone at the anatomical, vascular, cellular and molecular level. At the anatomical level, bone is at the inside in direct contact with the bone marrow and at the outside with structures that are involved in chronic inflammatory rheumatic diseases (entheses, periosteum, calcified cartilage). At the cellular and molecular level, many bilateral cross-talks between the immune system and bone have been described, in normal physiological conditions and during inflammation. In addition, in the presence of bone erosions at the sites of inflammation, direct contact is available between the bone marrow and the joint cavity.
Bone resorption is increased in RA. This has been demonstrated by the presence of activated osteoclasts in the pannus at the site of bone erosions and in subchondral osteitis.
The final cellular pathway of the attack of chronic or recurrent inflammation on bone is the recruitment and activation of osteoclasts. One of the central molecular pathways in this process is RANK ligand/OPG. In normal conditions, the osteoblast is the main regulator of bone resorption by this pathway. In rheumatoid arthritis, RANK ligand is also produced by inflammatory cells, including activated T- and B-cells, which are present in synovitis and in subchondral osteitis. By playing a central role in erosion formation, the osteoclast is not only responsible for functional handicap resulting from bone destruction at long term, but also for allowing the joint space to have direct access with subchondral bone marrow and its vast reserve of stem cells and B-cells.
Inhibition of osteoclasts by denosumab, a humanized antibody that selectively binds RANK ligand, has revealed that the occurrence of erosions and peri-articular bone loss can be halted, however without affecting synovial inflammation. This disconnect between inflammation and bone destruction opens new ways to separately focus treatment on inflammation and osteoclastogenesis for preventing and/or minimizing the connection between joints and subchondral bone and bone marrow.

A14

Pathophysiology of subchondral bone erosions in rheumatoid arthritis

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The presentation describes the novel insights on the interaction between the immune system and bone over the last 10 year, and explains molecular and cellular interactions as well as their clinical implications.
Bone is subject to a continuous remodeling process which allows an ideal adaptation to the individual demands throughout life. This remodeling process is based an interplay between bone forming osteoblasts and the bone resorbing osteoclasts. Several conditions alter this balance, among them the drop of estrogens levels after menopause is the most well known factor, which leads to enhanced bone resorption and bone loss. Interestingly, all different forms of inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease also interfere with the bone remodeling process and precipitate bone loss and increased fracture risk.
To study this interaction between immune activation/inflammation and the skeletal system has become a novel research discipline called osteoimmunology. This field has gained insights into the mechanism of inflammatory bone loss, in particular of how inflammatory cytokines like TNF-alpha, IL1 or IL6 foster bone resorption and inhibit bone formation, resulting in an imbalance of bone homeostasis and thereby precipitating bone loss. Therapeutic inhibition of cytokines has yields profound changes architecture in arthritis patients and protects the bone and in part also the articular cartilage. Inflammatory cytokines particularly enhance bone loss by activation of osteoclast differentiation factors such as MCSF and RANK ligand and by molecules which interfere with bone formation such as DKK1 and sclerostin.
The insights into molecular regulation of bone remodelling by the immune system are thus of key interest in better understanding inflammatory diseases such as arthritis and to shape novel therapeutic concepts. Research in the field of osteoimmunology has a strong translational approach and directly affects patients suffering from inflammatory diseases, in particular arthritis, in aiming to prevent skeletal damage and loss of physical function.

A15

Biologicals and bone loss

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Inflammatory joint diseases like rheumatoid arthritis (RA), as well as other rheumatic conditions such as ankylosing spondylitis and systemic lupus erythematosus, comprise a heterogeneous group of joint disorders that are all associated with extra-articular side effects, including bone involvement. Disease activity, immobility and treatment with glucocorticoids are the main factors that increase the risk of osteoporotic fractures, on top of the background fracture risk based on, amongst others, age, body mass index and gender. It is thought that the pathogenesis of both peri-articular and generalized osteoporosis and local bone erosions share common pathways. This hypothesis has been strengthened by the discovery that osteoclasts, stimulated mostly by the receptor activator of nuclear factor kappa B ligand (RANKL) pathway, play a central role in all of these processes.
Generalized bone loss has been documented in cross-sectional studies: a 2-fold increase in osteoporosis, defined as a T-score <−2.5 in females and Z-score <−1 was found in 394 postmenopausal RA-patients and 192 male RA-patients [1]. Before the introduction of biologicals, a high bone loss was also observed in a longitudinal study in early RA: −2.4% at the spine and −4.3% at the trochanter [2]. Against that background, it is relevant that we investigated whether treatment with anti-TNF-α prevents loss of bone mineral density at the spine and hip (generalized) and in the hands (local) in patients with rheumatoid arthritis (RA) and during anti-TNF treatment [3]. 102 patients with active RA, who were treated with infliximab during one year, were included into this open cohort study. The BMD of the spine and hip was unchanged during treatment with infliximab, whereas BMD of the hand decreased significantly by 0.8% ($p < 0.001$). The BMD of the hip in patients with an EULAR good response showed a favorable change compared with patients not achieving such a response. This is a proof that the usually occurring generalized bone loss in patients with RA can be arrested by the use of aggressive antirheumatic drugs, such as anti-TNF.
Next to BMD changes upon anti-TNF, we investigated the changes in bone markers, to elucidate the underlying mechanism of the favourable effect of anti-TNF. Bone formation was measured by osteocalcin (OC) and bone resorption was determined by b-isomerized carboxy terminal telopeptide of type 1 collagen (b-CTx); osteoclast regulating proteins including the soluble receptor activator of Nfκb (s-RANKL) and osteoprotegerin (OPG) were determined in serum using an ELISA from Immun-diagnostik. Serum β-CTx and RANKL were both significantly decreased compared to baseline at all time points. The decrease in β-CTx was associated to the decrease in DAS-28 and CRP during the 0 to 14 weeks interval. No changes were observed in serum osteocalcin and OPG. These data on bone mineral density emphasizes that the arrested bone loss at the spine and hips can be described to a large extent to a decrease in disease activity.
Later on, it was also shown that bone loss could be arrested in RA-patient treated with adalimumab [4], and the favourable effects of anti-TNF on bone markers were also observed during treatment with rituximab [5].

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A16

The role of bone morphogenetic proteins in ankylosing spondylitis

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Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-beta superfamily and were originally identified as proteins that induce a full cascade of endochondral bone formation in vivo and ectopically. We hypothesized that the BMP signaling pathway could also play a role in the process of ankylosis that characterizes ankylosing spondylitis and related spondyloarthritides. By over expression of noggin, a BMP antagonist, in a dedicated mouse model of joint ankylosis, we provided evidence for this hypothesis. Our current studies focus on the relationship between stromal cell activation and inflammation, a link that is essential in ankylosing spondylitis. Emerging functional and genetic evidence further corroborates the essential role of BMPs in these processes. BMPs can trigger different downstream signaling cascades, in particular Smad and p38 signaling. Inhibition of p38 signaling in vivo in the spontaneous ankylosing enthesitis model appears to accelerate ankylosis while inhibiting in vitro chondrogenesis. Genetic analysis of intercrosses between the susceptible DBA/1 strain and the H2 identical Balb/c strain point towards a region containing the BMP type Ib receptor as a factor determining genetic susceptibility. Recent clinical data suggest that levels of BMPs are higher in patients with progressive ankylosis in comparison with patients that show no structural progression of disease. Taken together, these data support our hypothesis that BMP signaling is a therapeutic target in ankylosing spondylitis.

A17

Epidemiology of osteoporosis and fractures in ankylosing spondylitis

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Osteoporosis and fractures, especially vertebral fractures, are a frequent complication of ankylosing spondylitis, even in the early stages of the disease. The risk of osteoporosis appears to be associated with elevated biochemical markers of bone turnover, increased pro-inflammatory cytokines, lower BMD, lower body weight and longer disease duration.
Using the WHO criteria (T score < −2.5), the prevalence of osteoporosis determined by BMD is about 29% in the spine and 12% in the hip in patients with ankylosing spondylitis, which compares with 2% and 1% respectively for controls. Although BMD is generally lower in patients with early disease, with progressive disease, the spine site becomes much less reliable due to the presence of syndesmophytes and periosteal new bone formation. In advanced cases, DXA becomes less reliable but using QCT, bone loss can be shown to continue within the vertebra and hips as well as an increase in cortical BMD and width.
The epidemiology of fractures in ankylosing spondylitis remains unclear although vertebral fractures have been most studied. The risk of clinical vertebral fractures is significantly increased (OR approximately 7.7 95% CI 4.3-12.6) and the cumulative incidence of clinical vertebral fractures is higher in men (OR 10.7 versus 4.2 in women) and increased especially during the first 5 years of the disease. The prevalence and incidence of non-vertebral fractures has been less well studied but in most reports appears to be about the same as in the control population.
Managing skeletal complications in anklosing spondylitis should include DXA of the spine and hip early in the disease. In more advanced disease, spinal DXA is not a useful predictor of fracture. In these circumstances, QCT should be considered. If a vertebral fracture is suspected, spinal imaging is required in order to avoid delays in diagnosis and therapy.

A18

Imaging of ankylosing spondylitis

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Conventional radiography can visualize bone erosion, sclerosis, joint space narrowing and new bone formation in sacroiliac joints and the spine, but is unfortunately not very sensitive in early disease. Diagnosis of ankylosing spondylitis (AS) is dependent on presence of bilateral moderate or unilateral severe radiographic sacroiliitis, as part of the modified New York criteria for AS. This has, until recently (see MRI below), delayed the diagnosis by 7-10 years. Furthermore, the modified Stokes ankylosing spondylitis spine score (mSASSS), which is the most sensitive radiographic method for monitoring structural damage in AS, is not very reproducible or sensitive to change, so improved methods for structural damage assessment are highly needed.
MRI has resulted in a major improvement in the evaluation and management of patients with SpA. Firstly, it permits earlier diagnosis, as MRI findings of active sacroiliitis form part of the recent ASAS criteria for axial spondyloarthritis. Secondly, MRI can provide objective evidence of currently active inflammation in patients with SpA. MRI is by far the best available method for detecting and monitoring inflammation in the spine and sacroiliac joints, and several validated assessment systems exist. Until the introduction of MRI, disease activity assessment was restricted to patient-reported outcomes, such as the Bath ankylosing spondylitis disease activity index (BASDAI) and functional index (BASFI), because disease activity could not be assessed in a sensitive manner by biochemical (mainly C- reactive protein (CRP)) or physical evaluation. Furthermore, MRI can visualize structural damage (erosion, fat infiltration, syndesmophytes and ankylosis) in the sacroiliac joint and spine, but the clinical role of MRI for monitoring structural damage remains to be established.
Finally, certain MRI findings (inflammation at the vertebral corners) have predictive value with respect to subsequent development of radiographic syndesmophytes. However, clarification of the prognostic value of MRI in clinical practice requires further research.
Despite contrast-enhanced Doppler US has been reported to have a high negative predictive value for the detection of sacroiliitis, the role of US in assessment of sacroiliac and spine involvement in AS and other types of axial SpA is minimal.

A19

Why and how to optimize glucocorticoid treatment in rheumatoid arthritis

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Glucocorticoids (GC) are the most potent anti-inflammatory and immunosuppressive hormones mainly produced by the adrenal glands in humans.
The central nervous clock system, under the influence of light/dark alternation, "creates" the internal circadian rhythms and the organisms by "feeling" these rhythmic external changes, synchronize their physical activities, including sleep, related nocturnal hormone synthesis and immune function [1].

As a matter of fact, GC rise during the night around 3 am and start to exert anti-inflammatory and immunosuppressive activities. On the other hand, the nocturnal pineal hormone melatonin, that rises earlier in the night with darkness, has been linked to chronic inflammation since at normal to slightly elevated concentrations stimulate many aspects of the immune/inflammatory response, especially at the level of macrophages [2].

The immune-supportive role of melatonin and the reduced immune suppression linked to decreased endogenous GC (due to the chronic stress of the disease) have been delineated in the context of the circadian rhythms of immune/inflammatory reaction and related clinical (morning) symptoms, at least in RA [3].

Therefore, the most advanced approach to optimize the risk-benefit ratio of long-term low-dose GC treatment is the GC-chronotherapy, using a modified release (MR) prednisone (release during the night) and following the circadian rhythms.

In fact in RA, the circadian rhythms of clinical symptoms are more evident in the early morning hours, since preceded by nocturnal elevated levels of pro-inflammatory cytokines (i.e.IL-6). Therefore, since prevention of nocturnal rise of pro-inflammatory cytokines by GC therapy would be more effective than treating established symptoms in the morning and might reduce doses and side effects, a MR prednisone was developed, which releases prednisone approximately four hours after ingestion (i.e., at approximately 2-3 am when taken at bedtime) [4]. In addition to all recognized therapeutic effects obtained with conventional prednisone, MR prednisone was shown to have similar profile of adverse effects but without additional suppression of hypothalamic-pituitary-adrenal (HPA) axis [5].

In conclusion, night-time low dose long-term GC therapy in chronic rheumatic diseases such as RA, is today considered as an "hormonal replacement therapy" that optimally implement the peripheral insufficiency of endogenous GC in modulating the immune/inflammatory reaction.

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