ACR/ARHP Annual Meeting 2017

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PEER-REVIEWED CONFERENCE REPORT

Late Breakers

Possibly disease-modifying drugs in osteoarthritis played a key role during this year's Late Breaker; a recombinant human fibroblast growth factor was able to improve cartilage thickness. The cathepsin K inhibitor MIV-711 was able to diminish bone disease progression.

read more on PAGE 3

Rheumatoid Arthritis (RA)

Comorbidities are still underestimated in this vulnerable patient group; established RA patients have a comparable cardiovascular risk as diabetics. Early onset atherosclerosis is another problem rheumatologist should be aware of.

read more on PAGE 8

Systemic Lupus Erythematosus (SLE)

Life style factors are of key importance in the management of SLE; obese patients have worse treatment outcomes, and nutrition counseling showed to be effective regarding improvement of quality of sleep.

read more on PAGE 19

MEDICOM MEDICAL PUBLISHERS

Editor Prof. dr. Robert J. Moots, University of Liverpool, United Kingdom

Contents

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Letter from the Editor

Professor Robert J. Moots MD PhD

Dear Reader,

Welcome to this review of the 2017 ACR meeting, held in San Diego. This meeting is a great opportunity to catch up on the many developments occurring in Rheumatology over the past 12 months, with cutting edge talks from international leaders. However, many do not get the chance to attend this meeting – and others might have been there, but unable to attend all sessions of interest due to clashes in the programme, or simple exhaustion with the extensive schedule. Whether you are in one of these groups, or just want to revise what you learned in San Diego – this review is for you!

We have assembled reports from key areas discussed in the 2017 ACR meeting, to give you a broad view of what has been presented. There topics selected range from late breaking abstracts with data on the use of novel agents such as Sprifermin in degenerative joint disease, through discussing perhaps unexpected links between obesity and inflammation, to "State of the Art" talks on rheumatoid arthritis. Whatever your interests in rheumatology, I am sure that you will find something here that will stimulate you and hope that you will enjoy reading this excellent and helpful review.

Best wishes
Robert Moots

Biography

Robert Moots is Professor of Rheumatology at the University of Liverpool. Qualifying in Medicine in London, he earned his PhD in immunology at the University of Oxford UK and worked at Harvard Medical School before returning to the UK to establish a new research group in Liverpool.

His research focuses on inflammatory diseases, from bench to bedside. He has published extensively, advises NICE, is Past Editor of Rheumatology and lectures all around the world. His group is EULAR Centre of Excellence. Clinical service remains important and his unit is a National Referral Centre.

Late Breakers

Only the most interesting posters and abstracts were accepted as late breakers. Many new data dealt with osteoarthritis (OA) for the first time, disease-modifying drug might be close at hand.

Improvement of cartilage thickness

Sprifermin is a recombinant human fibroblast growth factor 18 and is currently under investigation as a potential disease-modifying OA drug. Experimental data has shown that it binds and specifically activates fibroblast growth factor receptor-3, in cartilage to promote chondrogenesis and cartilage matrix production, in vitro [1]. In addition, sprifermin stimulates chondrocyte proliferation in experimental studies. The two-year data from the 5-year phase II trial (FORWARD) were presented as a late breaker [2]. In this trial, 549 patients with symptomatic radiographic knee OA were given 3 weekly intra-articular injections of either placebo or sprifermin every 6 or 12 months. The primary study endpoint was the change in total tibiofemoral joint (TFJ) cartilage thickness over 2 years. Injections with sprifermin led to a dose dependent increase in TFJ cartilage thickness. In addition, cartilage thickness in both, central medial and central lateral TFJ sub-regions increased (Figure 1)

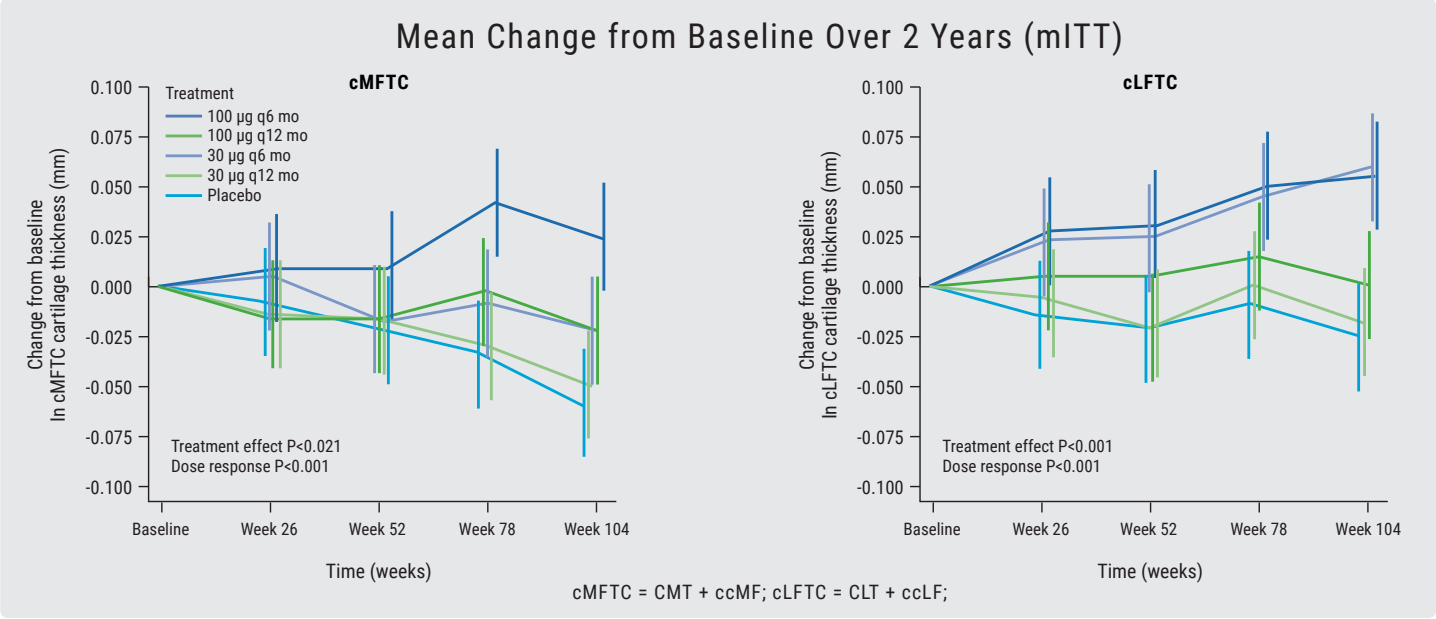
Total Western Ontario and McMaster Universities Arthritis Index (WOMAC) score was evaluated as a secondary endpoint. All the treatment groups including placebo had a mean decrease by 50% in total WOMAC score.

"We choose a total duration of five years for this trial, because we hope that there is also an influence on pain after 3 to 5 years. In addition, it is difficult to show differences in pain, because all our patients were allowed to use analgesics", said Dr. Marc Hochberg, University of Maryland Medical Centre, Baltimore (USA).

The most frequent treatment emergent adverse events (TEAEs) were musculoskeletal and connective tissue disorders (arthralgia, back pain). In addition, there was no difference in the rates of TEAEs leading to discontinuation between sprifermin and placebo. More patients in the sprifermin group, had side effects compared to placebo, but the increase was only significant in the first injection cycle.

According to Dr. Hochberg, sprifermin could be the first investigational medicinal product to show dose-dependent prevention of cartilage loss and an increase in cartilage thickness, not only in the total TFJ, but also in both the medial and lateral compartments, including the central medial femorotibial region. These structural benefits associated with sprifermin suggest that it may be efficacious

Figure 1 Secondary endpoint of the FORWARD trial: therapy with sprifermin leads to an increase of cartilage thickness. [2]



as a structural and disease – modifying OA drug with an acceptable benefit-risk balance.

Is there a new promising opioid analgesic?

In a phase 2b trial, the selective kappa opioid receptor agonist CR845 was investigated on moderate osteoarthritic hip or knee pain, in over 470 adults [3]. The agent was started with 1.0 mg and then up titrated over 4 weeks to 2.5mg or 5.0 mg (Group 1 and 2) and compared to a 3rd group, that received placebo. The primary endpoint of greater change in the pain intensity, in the index joint compared to placebo over 8 weeks was not met. Nevertheless, patients with hip OA, those were treated with 5.0 mg of CR845, experienced a significant advantage over placebo with 69 % pain reduction in their mean joint pain score in post-hoc evaluation. Moreover both, knee and hip patients on the highest dose judged their status meaningfully more often as "very much" or "much" improved. As to be expected, an opioid receptor agonist, constipation, dizziness and dry mouth were among the common adverse events of CR845.

MIV-711 slows osteoarthritis progression

Individuals with focal cartilage lesions show elevations of C-terminal telopeptide of collagen. These are created during articular cartilage breakdown and therefore considered as a biomarker of OA [4]. Another trial presented during the meeting, the cathepsin K inhibitor MIV-711, induced a reduction of this collagen degradation product in healthy volunteers [5]. Therefore, MIV-711 was tested in 244 OA patients at 6 different sites in Europe regarding a possible disease modifying effect [5]. All participants suffered from knee OA with a Kellgren and Lawrence score of 2-3 and pain between values of ≥4 to ≤10 on a nume

ric pain rating scale (NRS) from 0-10. After randomisation, patients received daily 100mg (n=82), 200 mg (n=82) MIV-711 or placebo (n=80), daily over 26 weeks. Primary outcome was defined as modification of NRS score, but focus was also set on changes of MRI findings e.g. of the medial femur. Participants had a mean age of 62, BMI of 32 kg/m2 and most of them were female. The primary endpoint was not met, but interestingly MIV-711 diminished bone disease progression as well as loss of cartilage with both doses, compared to placebo. According to the investigators, the study duration was probably too short to reveal symptom amelioration due to modified joint structures.

Less pain after phosphoglycoprotein injections

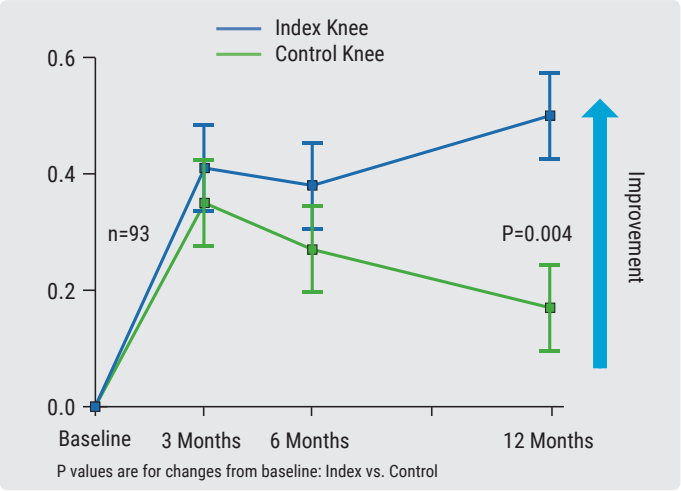
118 patients with OA of the patellofemoral joint of both knees were included in a trial, to evaluate the efficacy as well as safety of the 23-amino acid peptide TPX-100 in a proof of concept randomised controlled trial (RCT) [6]. TPX-100 is a derivate of matrix extracellular phosphoglycoprotein. This glycoprotein plays an important role in biomineralisation and has exerted post-injury proliferation of cartilage in animal models. 236 knees were treated with intraarticular TPX-100 in 4 weekly injections using 20, 50, 100 or 200mg/injection in the different randomised groups. Results were evaluated using the Knee Osteoarthritis Outcomes Score. Median age of study subjects was 60 and Body Mass Index (BMI) was 29.2 kg/m2, both being typical features of OA patients in the USA. Control MRIs after 6 and 12 months of treatment were unable to detect between-knee-differences in volume of cartilage, but clinical function including activities of daily living, sports activities, and knee-related quality of life improved significantly. In addition, pain while climbing or descending stairs improved significantly in the TPX-100 treated knees (Figure 2). Use of NSAIDs decreased by 62.5% during the study.

Adverse events did not differ between treated knees and control knees. Considering these results, the authors conclude that TPX-100 warrants further investigation for treatment of OA.

Risankizumab highly effective in psoriatic arthritis

Risankizumab is a monoclonal antibody that inhibits IL-23 by specifically binding to its p19 subunit. This cytokine is a key regulator of multiple effector cytokines that has been implicated in psoriatic skin lesions, synovitis, enthesitis, and bone remodeling. It proved to be highly efficacious in the treatment of psoriasis. During the ACR meeting, a phase II trial in patients with psoriatic arthritis according to the Classification Criteria for Psoriatic Arthritis (CASPAR)

Figure 2 Change in KOOS pain while moving up or down stairs. [6]



was presented [7]. All patients had at least one psoriatic lesion or a documented history of psoriasis. 185 patients with active PsA (defined as ≥ 5 tender joints and ≥ 5 swollen joints) were randomized to five treatment arms: placebo, a single subcutaneous 75-mg injection of risankizumab at week 0; 150 mg at weeks 0 and 12; 150 mg at weeks 0, 4, and 16; and 150 mg at weeks 0, 4, 8, 12, and 16. These last two groups were pooled as well as reported individually.

Primary endpoint was a 20% reduction according to the criteria of the American College of Rheumatology (ACR 20 response) at week 16: 60% of patients receiving either three or five doses of 150 mg risankizumab reached this endpoint, compared with 36% of a placebo group (Figure 3). Accordingly, more patients in the risankizumab groups reached an ACR 50 and ACR 70 response. Responses were more pronounced in TNF naive compared to TNF experienced patients.

As in previous trials, skin symptoms showed a dramatic improvement: 67%-75% of patients in the active drug arms achieved a reduction in Psoriasis Area and Severity Index (PASI) by 75% compared to 10% of the placebo group. 52-67% of patients treated with risankizumab achieved nearly clear skin (PASI 90 responses) vs. 7% of those on placebo. Proportions of patients achieving ACR20 and PASI75 response increased steadily through the 16 weeks of treatment and follow-up. Risankizumab was also superior in several secondary outcomes, e.g. change in the Health Assessment Questionnaire Disability Index (HAQ-DI) score or achievers of minimal disease activity (MDA) at week 16. In addition, there was a marked reduction of pain, assessed in a visual analogue scale (VAS) in patients treated with risankizumab. The only outcome where at least one risankizumab dosing group did not improve significantly more than the placebo group was change in dactylitis count.

Favorable safety profile

About a fifth of patients in each group, including placebo, had adverse events considered drug related. There was a total of 10 serious adverse events, four in the placebo group and three of the other six in the highest-dose risankizumab arm. "With this positive result, phase III studies are under way, but dosing will be decided when data through week 24 from this phase II study are fully analyzed", said Prof. Philip J. Mease, Swedish Medical Centre, Seattle (USA).

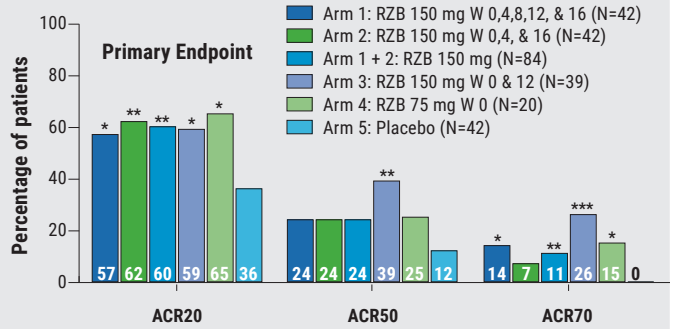
Secukinumab decelerates radiographic progression in psoriatic arthritis

New data showed the ability of the fully human monoclonal IL-17 inhibitor secukinumab to slow down radiographic progression in patients with psoriatic arthritis (PsA) [8]. In his talk, Prof. Philip J Mease, Swedish Medical Centre and University of Washington, Seattle, USA stressed that secukinumab with its selective neutralisation of IL-17A, has already shown significant efficacy with rapid onset of action in PsA in the FUTURE 1 and 2 trials.

During this year´s meeting, current data indicated that secukinumab is also able to reduce structural disease progression. With nearly 1000 patients, the FUTURE 5 trial is the largest randomized controlled trial (RCT) of a biologic conducted to date in PsA. In FUTURE5, the efficacy of secukinumab to inhibit radiographic progression of structural damage was evaluated as a secondary study endpoint. Radiographic structural progression was measured by modified total van der Heijde Sharp score (mTSS), assessed by two blinded readers, based on hand/wrist/foot X-rays.

Radiographic progression (mTSS) was significantly inhibited at week 24 in all secukinumab arms (150 mg or 300 mg with or without loading dose) vs. placebo. Patients treated with secukinumab also showed an impressive improvement in enthesitis and dactylitis. "This means a lot for our patients. Enthesitis of the Achilles tendon is a major functional impairment", said Prof. Mease. Efficacy across all endpoints was greater in patients who were anti-TNF-naive. In addition, patients treated with secukinumab showed an up to 62% improvement of American College of Rheumatology (ACR) 20 response at week 16 (primary study endpoint).

Figure 3 ACR responses at week 16 with different doses of risankizumab and placebo. [7]



P-values for comparison vs placebo: ***, P<0.001; **, P<0.01; *, P<0.05; no multiplicity adjustment; NRI= non-responder imputation; W = week.

Tofacitinib does not elevate thromboembolic events

Previously there have been concerns regarding the safety of JAK 1 and 2 inhibitors due to their potential risks of venous thromboembolism. Therefore, data from phase 2 and 3 RCTs with tofacitinib treatment were analyzed with regard to these

side effects [9]. The included trials investigated tofacitinib as mono- or combination therapy for RA, psoriasis (PsO), PsA and ulcerative colitis. Two cohorts were defined: one consisted of those of tofacitinib vs placebo, the other of tofacitinib vs. adalimumab or methotrexate. Incidence rates (IR) of previously defined deep vein thrombosis (DVT) and pulmonary embolism (PE) were based on the occurrence of single events ≤ 28 days after the last drug administration or up to the cohort cut-off date. IR were compared with those from the Corrona Registry with real world data on more than 40,000 enrolled RA patients [10].

The two cases of DVT and PE within the placebo controlled trials both happened under placebo. IR of DVT in the dose-comparison cohort was identified as 0.1 for tofacitinib in RA and 0.5, for tofacitinib in PsA (in a dose of 10 mg given twice daily (BID) in both indications). In the same cohort, all 5 cases of PE occurred in RA, equaling an IR of 0.1 with tofacitinib 5mg BID and 0.2 with a dose of 10mg BID. As these events are in the same order of magnitude as those within the Corrona Registry, the study authors concluded that there is no evidence of an increased risk for thromboembolic events under tofacitinib.

IL-17A inhibition: slower progression in AS

At present, there is an unmet need for disease-modifying therapies that can reduce progression in patients with ankylosing spondylitis (AS). Structural progression in AS is characterized by new bone formation, and can lead to ankyloses of the sacroiliac joints and the spine [11]. In the MEASURE 1 trial, secukinumab demonstrated sustained improvements in signs and symptoms of AS through two years. 80% of the participants had no structural progression [12,13]. Dr. Jürgen Braun, Rheumazentrum Ruhrgebiet, Herne (Germany), presented the 4-year results of the MEASURE 1 study, that included imaging outcomes [14]. Nearly 90% of those assigned to secukinumab 150 mg completed 208 weeks of treatment. To evaluate sustainability of secukinumab benefits through week 208, different indices (e.g. Assessment of Spondyloarthritis International Society (ASAS) 20/40 response, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), among others) were used. Sustained ASAS responses, and other indices, were seen through 4 years. In addition, C reactive protein (CRP) levels remained lower throughout the extension study.

Approximately 80% of patients had no radiographic progression (assessed with the modified Stoke Ankylosing Spondylitis Spine Score) on treatment with secukinumab over 208 weeks (Figure 4). "This is the first study reporting the long-term effect of secukinumab on radiographic structural progression in AS", said Dr. Jürgen Braun during the presentation of the data. Earlier observational and interventional studies with anti-TNF blockers had numerically higher progression rates [15].

First specific medication for IgG4-related disease

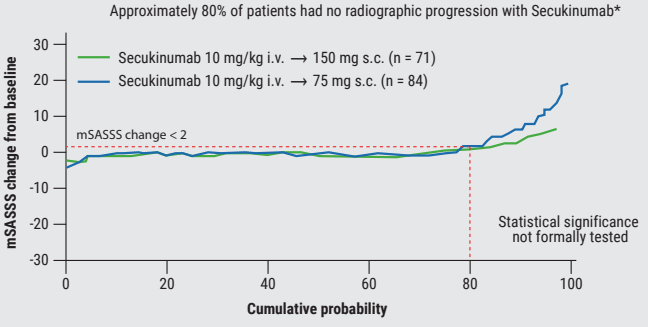
IgG4-related disease is a rare B-cell disorder that affects multiple organ systems. It mimics many other rheumatic diseases, e.g. Sjogren's and lupus. At present, there is a high need for specific effective treatment, because patients are currently only treated with corticosteroids or rituximab.

An open-label phase II pilot provides a glimpse of hope for these patients. The study lasted 6 months and involved 15 patients and was presented by Prof. John H. Stone, Massachusetts General Hospital, in Boston (USA) [16]. Of 15 patients with the often-fatal condition, eight achieved remission after 2 months of treatment with the reversible B cell inhibitor Xmab-5871, an anti-CD19 monoclonal antibody. The agent inhibits many activation pathways in both healthy and diseased B cells and suppresses B cell responses without destroying B cells.

In the current trial patients received the drug by infusion, every two weeks for a total of 24 weeks. The primary outcome measure was a minimum 2-point reduction from baseline in the multi-component IgG4-Related Disease Responder Index. This was adapted from the Birmingham Vasculitis Activity Scale and the ANCA-Associated Vasculitis Scale. 13 patients had at least three organs involved.

The drug had a quick onset of action as seen in sharp drops in mean B-cell and plasma blast counts, after the second dose. 14 patients (93%) achieved a decrease of at least 5 points or more at some time in the study. 12 patients (80%)

Figure 4 MEASURE 1 trial: sustained low radiographic progression during treatment with secukinumab. [14]



mSASSS, modified Stoke Ankylosing Spine Score; n, number of patients with assesments at Baseline and Week 208
* No progression was defined as a mSASSS change < 2 from Baseline to Week 208

completed the study. All of them met the primary endpoint of an at least 2 points reductions at day 169. Eight of these 12 patients achieved remission at day 169 defined as a score in the multi-component responder index of ≤ 4 at day 169 and no corticosteroids after month two (all organs improved). All five patients on corticosteroids at baseline were tapered off within two months. "XmAb5871 shows promising activity in IgG4-RD", concluded Prof. Stone.

Ustekinumab: also, effective in systemic lupus erythematosus

The IL-12/23 inhibitor ustekinumab is also effective in patients with active Systemic Lupus Erythematosus (SLE). This showed the results of a phase II, randomized placebo-controlled study. "There is an unmet clinical need regarding therapy of SLE", said Dr. Ronald van Vollenhoven, Amsterdam Rheumatology and Immunology Centre ARC (The Netherlands) [17]. Both IL-12 and IL-23 appear to have a role in SL, IL-12 through its part in TH1 cell development and cytotoxic T cell activation, and IL-23 for driving pathogenic TH17 cell expansion, which is believed to be a key player in tissue inflammation. The trial included 102 patients with active SLE, most of them were treated with steroids and many with antimalarial.

The primary endpoint was achievement at week 24 of the so-called SRI-4, a composite of a 4-point or greater decrease in SLE Disease Activity Index (SLEDAI) score, no worsening in physician global assessment, no new BILAG (British Isles Lupus Assessment Group) A flares, and no more than one new BILAG B event. This endpoint was met by 60% of patients assigned to ustekinumab compared to 31% of the placebo group (P=0.0046). Greater proportions of patients in the ustekinumab group showed improvement in joint and mucocutaneous disease compared to placebo.

"We believe this phase II clinical trial shows ustekinumab has the potential to be a new treatment in SLE with a novel mechanism of action," concluded Dr. van Vollenhoven.

Ustekinumab is currently approved for psoriasis, psoriatic arthritis, and Crohn's disease.

Biologics don't increase the risk of second malignancy

Since biologic disease-modifying anti-rheumatic drugs (bDMARDs) became a mainstay of successful management of rheumatic diseases starting about 15 years ago, not only knowledge about efficacy has accumulated, but also reliable data about side effects and potential risk is accessible. The question whether biologics increase the risk for another malignancy in cancer survivors has yet not been unanimously answered.

A Danish population-based cohort study by Prof. Lene Dreyer, clinical medicine, Gentofte University Hospital, Hellerup (Denmark) and her team analysed data from the Danish Cancer registry dating from 2000-2011, identifying 1678 patients with rheumatoid arthritis (RA) and comorbidity of a primary cancer [18]. Amongst them were 502 patients that took biologic DMARDs (bDMARDs) before and/or after their cancer diagnosis. The cancer site adjusted hazard ratio (HR) for developing a second malignant neoplasm was calculated with 1.11 for bDMARD treated patients in comparison to those who never had a bDMARD therapy. During further investigation with view to the time of bDMARD administration this hazard ratio changed to 1.06 in bDMARD before first cancer only users, 1.15 in after first cancer only users and 1.09 in before and after first cancer users of bDMARDs. The authors conclude from this data that RA patients with a history of cancer have no increased risk of a secondary neoplasm when they are treated with bDMARDs compared with never treated patients.

Imaging of activated macrophages

As is already known, activated macrophages hold a central role in the pathogenesis of RA in the synovium because they can release TNF-alpha and consecutively support inflammation [19]. The aim of a small dose escalation study by Prof. Arash Kardan, nuclear medicine, Kettering Medical Centre, Kettering (USA) and his colleagues was to test a synthetic agent for radiopharmaceutical imaging with regard to safely depicting information about joint inflammation. Tc99m tilmanocept was given intravenously to patients with RA as it binds to activated macrophages with high affinity. None of the tested doses led to adverse events. The radiotracer demonstrated specific activity that could be shown by gamma emission imaging and also Single-Photon Emission Computed Tomography/ Computed Tomography (SPECT/CT) in RA affected joints like proximal interphalangeal joints and metacarpophalangeal joints, but not in cortical bone. Although only 9 patients have been tested Tc99m tilmanocept maybe of future interest due to its high specificity of activated macrophages.

New JAK-1 inhibitor shows distinct activity in RA patients

The new oral JAK-1 inhibitor upadacitinib was given in doses of once daily 15 or 30 mg in a phase III trial, with nearly 500 RA patients [20]. They had a mean disease duration of 13 years and showed insufficient response to prior DMARDs.

Primary endpoint was defined as the rate of patients reaching a reduction in disease activity of ≥20% (ACR20) and those with Disease Activity Score 28 joint count C reactive protein (DAS28-CRP) ≤3.2 compared to placebo. 53% of the patients had a history of treatment with ≥2 biologics.

ACR20 response was achieved by 64.6% of patients taking the low dose and by 56.4% taking the high dose of upadacitinib compared to 28.4% in the placebo group. Already after 1-week ACR20 was found in 27.4 % and 24.8% of the upadacitinib groups. This resulted in meaningful changes of the Health assessment questionnaire disability index (HAQ-DI). Adverse events (AE) occurred in 55.5% (15mg UPA) and 67.3% (30mg UPA) vs 56.2% under placebo. Serious AE only happened in the UPA groups, more precisely in 4.9% of the patients treated with the lower dose and 7.3% of the subjects under 30mg UPA. These adverse events are in line with those seen in the previous phase II trials. The authors conclude that upadacitinib leads to rapid and significant improvements in the sign and symptoms of RA in this treatment-refractory population.

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Rheumatoid Arthritis: State of the Art

Comorbid conditions are frequent in rheumatoid arthritis patients and have to be considered. Many trials addressed comorbid factors, and new ways to improve management of RA patients.

Autoimmune disease: similar cardiovascular risk as diabetes

Established RA is associated with a doubled cardiovascular (CV) risk [1]. Most rheumatologists do not screen patients for hypertension, lipids, and other cardiovascular risk factors even though patients with rheumatoid arthritis (RA) and other autoimmune diseases have an increased risk for cardiovascular disease. "The inflammation that comes with autoimmune disease, increases the risk of cardiovascular disease in itself," said Dr. Rekha Mankad, Director of the Cardio-Rheumatology Clinic at the Mayo Clinic in Rochester (USA) [2]. "That is on top of more familiar risk factors such as elevated blood pressure and lipids or obesity, which tend to be undertreated in the autoimmune population." Mounting evidence suggests that patients with autoimmune disease are at increased risk for cardiovascular disease in the same way that of patients with diabetes. When cardiovascular disease does occur, it is about a decade earlier than would be expected in the general population. Cardiovascular comorbidities have also gained importance due to the clinical success of rheumatology in treating rheumatologic disease: Patients are surviving longer and develop heart disease.

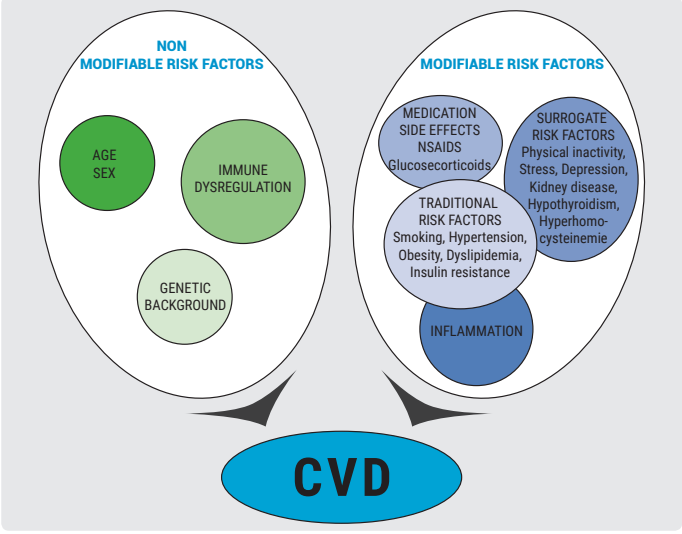
Systemic inflammation fuels early atherosclerosis

Dr. Mankad's group has been screening rheumatologic patients for cardiovascular risk and has seen surprising levels of atherosclerosis in patients younger than 65. Traditional risk factors such as hypertension, smoking, dyslipidemia and obesity contribute to the endothelial dysfunction in RA but cannot fully explain the high magnitude of CV disease at such an early age [3]. Systemic inflammation is probably the main driver of this elevated risk: it contributes to the initiation and development of accelerated atherosclerosis since inflammatory processes in the rheumatoid synovium

and atherosclerotic plaques are remarkably similar [4]. Proinflammatory cytokines such as TNF-alpha and IL-6 lead to endothelial dysfunction, the initial step to atherosclerosis [5]. In summary, there are complex interrelations between several risk factors in the development of premature atherosclerosis in RA [Figure 1) [6]. "The real question is whether there is a role for being more aggressive," she said. According to the recommendation of the "European League Against Rheumatism (EULAR)", annual CV risk assessment using national guidelines is recommended for all patients with RA. In addition to CV risk factor management, aggressive suppression of the inflammatory process is recommended to further lower the CV risk [7]. The question, whether anti-inflammatory treatment can lower the CV risk was also addressed in an oral presentation during the meeting [8]. Some data indicates that TNF blockers are more likely to be beneficial than harmful with regard to the risk of heart failure [9]. "The recent data suggest that anti-TNFs can be used safely in patients with mild chronic heart failure, but it's still something to consider when treating a patient with any history of chronic heart failure," said Prof. Katherine P. Liao, Harvard University Medical School and Brigham and Women's Hospital in Boston (USA). A cardiologist should be consulted before starting these patients on anti-TNFs.

In the TARGET trial, the triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) will be compared vs. methotrexate plus TNF inhibitor to determine the impact of either strategy on cardiovascular risk. "We've been pretty certain for some time now, based on what we've seen in large observational studies, that reducing inflammation reduces cardiovascular risk, but it's never actually been tested in a randomized controlled trial," Dr. Liao said. "This study will help us definitely answer that question", concluded Prof. Liao.

Figure 1 Complex interrelations between several risk factors in the development of premature atherosclerosis in RA. [6]



RA patients have not only a high risk for cardiovascular disease, but also an elevated risk to develop diabetes compared to the general population. According to data from the literature, the prevalence of diabetes among patients with RA has been reported as 7 to 25% [10-12].

RA patients may exhibit both, reduced insulin sensitivity and impaired pancreatic beta-cell function [13]. In a trial, RA patients had comparable metabolic parameters, decreased insulin sensitivity and β-cell function as compared with healthy controls, independent of their chronic glucocorticoid intake [13].

IL-6 elevates risk for type 2 diabetes

The proinflammatory cytokine IL-6 could be the link between RA and diabetes, it is involved in glucose metabolism and has been found to be increased in type 2 diabetic subjects [14]. Elevated CRP and IL-6 levels are an independent risk factor for type 2 diabetes and support a possible role for inflammation in diabetogenesis [15]. Previous studies showed that IL-6 receptor blockade enhances insulin sensitivity, suggesting that elevated IL-6 levels in type 2 diabetic subjects might be causally involved in the pathogenesis of insulin resistance [14,16]. Furthermore, inhibition of IL-6 signaling decreased Lp (a) serum levels, which might reduce the cardiovascular risk of human subjects [14].

"With this data in mind we conducted a post hoc analysis from 2 phase III trials, MOBILITY and TARGET", said Prof. Mark Genovese, Stanford School of Medicine, Stanford (USA) [17]. In these trials, the efficacy and safety of sarilumab, a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6-mediated signaling was assessed in patients with moderate to severe rheumatoid arthritis. In both trials, sarilumab reduced disease activity and improved signs and symptoms of RA, in the MOBILITY study, sarilumab also inhibited radiographic progression [18-19]. In the new analysis, patients with baseline and at least one post-baseline blood sample were included and categorized as diabetic or non-diabetics based on medical history of diabetes or prior use of antidiabetic medication. Only data collected during the placebo-controlled period were analyzed. Changes from baseline in fasting glucose, HbA1c, and weight were analyzed with a linear regression model.

Sarilumab improves impaired glucose metabolism

Mean fasting glucose and HbA1c at baseline were similar across treatment groups, but higher in the diabetes group than in the non-diabetes group. Decreases in HbA1c occurred

in all patients treated with sarilumab together with disease-modifying antirheumatic drugs (Figure 2). "In diabetic patient's curves diverged at week 12, but interestingly, we see the same trend in non-diabetics", said Prof. Genovese. Likewise, sarilumab reduced fasting blood glucose in diabetic patients [17]. Average increase in body weight was < 2% and similar in diabetic and non-diabetic patients.

Changes of HbA1c were independent of baseline oral glucocorticoid use or clinical response to treatment with sarilumab. "We do see improvements and I think they have clinical relevance: IL-6 interruption of signaling might be the cause", concluded Prof. Genovese. However, as in the study no clamp testing was done, the reason for this improvement is yet unknown. Therefore, a fully designed diabetic study might be of interest to elucidate the mechanism of action of IL-6 receptor blockade on glycemic control and the relevance of these preliminary findings for patients with RA and diabetes.

The new data shown during the ACR/ARHP demonstrate that the IL 6 blocker sarilumab might be particularly beneficial for patients with impaired glucose metabolism.

Switch from TNF-Blockade to IL-6: a successful therapeutic strategy

Patients that switched from adalimumab to sarilumab benefit regarding different efficacy and safety endpoints this showed an analysis of patients that completed the MONARCH trial and entered OLE, the open label extension trial of MONARCH [20]. IN MONARCH, efficacy and safety of sarilumab vs. monotherapy with adalimumab was assessed over 24 years in RA patients intolerant of, or inappropriate for or inadequate responder to MTX. Primary study endpoint of MONARCH was change from baseline in Disease Activity Score (28 joints, DAS 28) and erythrocyte sedimentation rate (ESR). Additional prespecified endpoints included proportion o of patients achieving American College of Rheumatology (ACR) 20% improvement criteria, and change from baseline in Clinical Disease Activity Index (CDAI). In the open label extension, OLE all patients received sarilumab 200 mg every 2 weeks. 155 patients from 320 who entered the OLE switched from adalimumab to sarilumab, compared with 165 patients that remained on sarilumab (continuation group). Patients that switched from adalimumab demonstrated improvements in physical function and in the signs and symptoms of RA, which became numerically similar to patients in the continuation group.

Positive long-term treatment results in tocilizumab switchers

Another post-hoc analysis presented during the ACR meeting assessed the outcome of patients that completed the ASCERTAIN trial who were switched to the open label extension study EXTEND [21]. ASCERTAIN was a 24-week, randomized, double-blind study that assessed safety and tolerability of sarilumab and tocilizumab, each added to conventional synthetic disease-modifying antirheumatic drug (csDMARD) background therapy, in patients with RA and inadequate response to or intolerance of tumour necrosis factor (TNF)

Figure 2 Therapy with sarilumab and DMARDs is associated with decreased HbA1c levels at 24 weeks in diabetic and non-diabetic patients. [17]

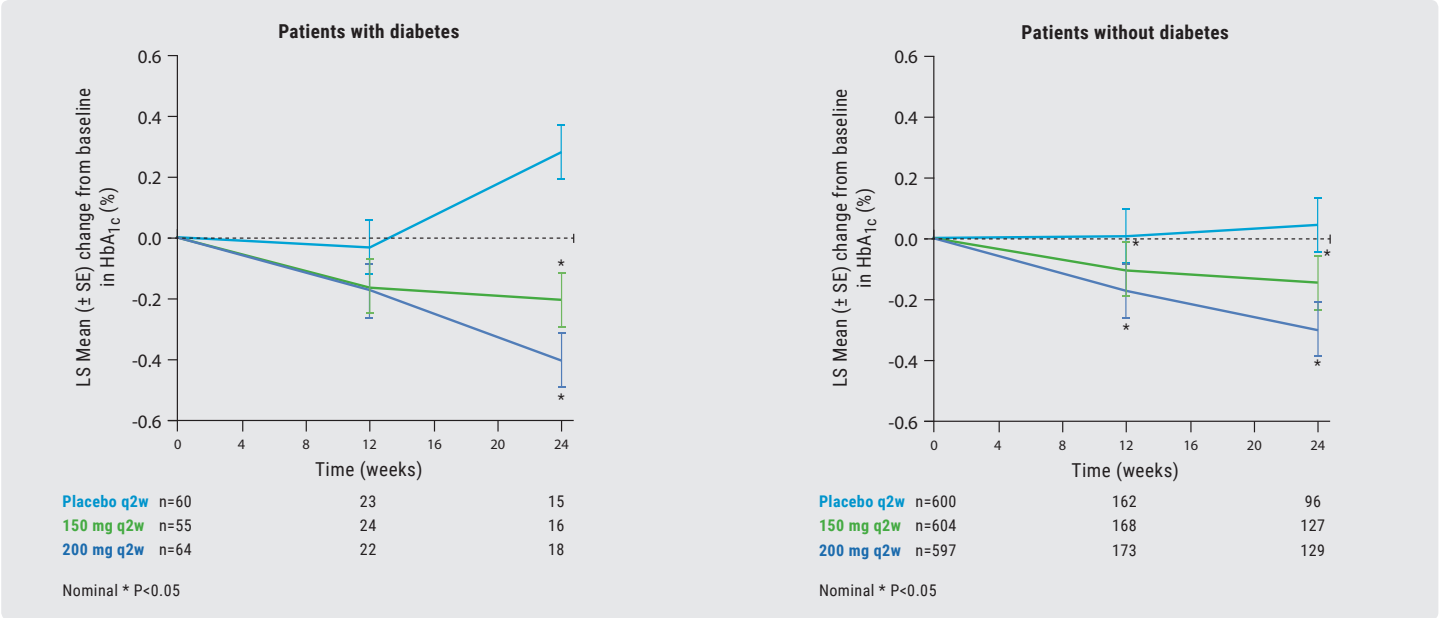
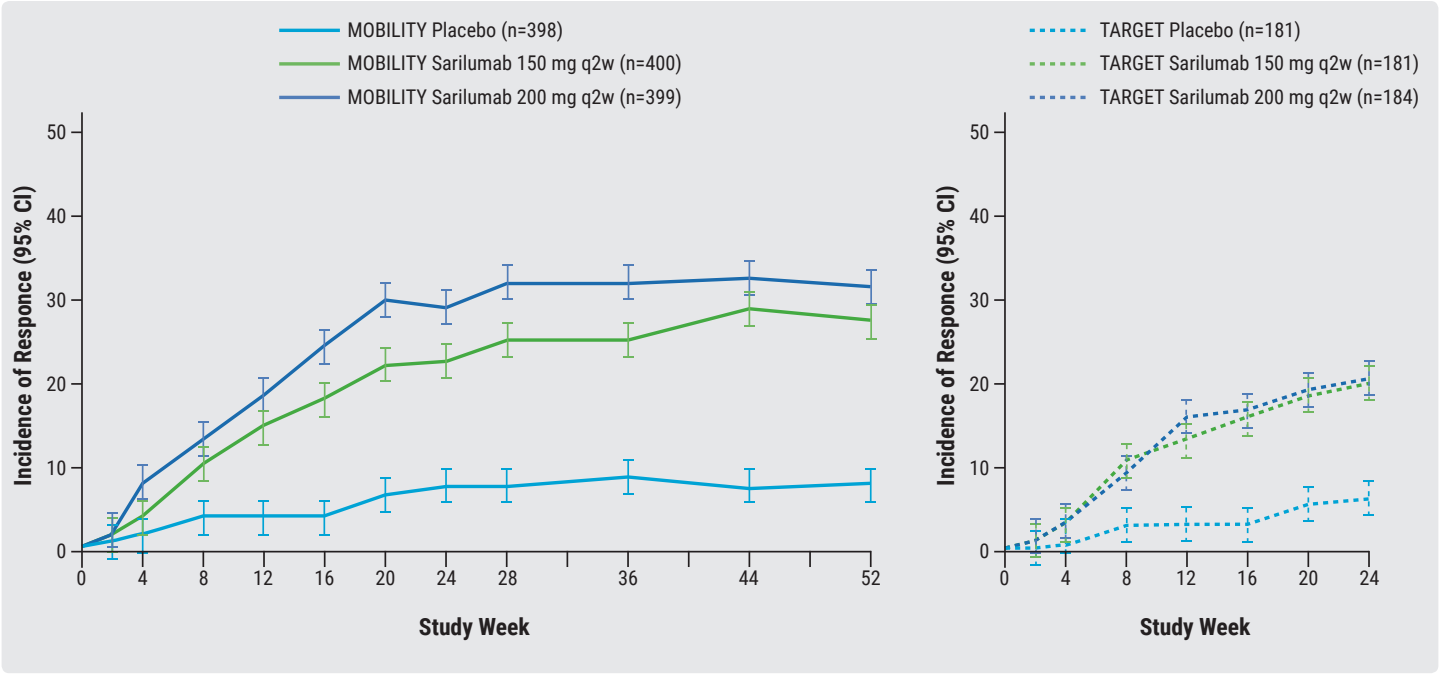


Figure 3 Ongoing effects of sarilumab on remission and LDA over time after treatment initiation (intent-to-treat populations) shown by patients achieving remission or LDA on DAS28-CRP <2.4 [22]



inhibitors. After completion of ASCERTAIN, patients were eligible to enroll in the uncontrolled extension trial EXTEND and receive open-label sarilumab 200 mg, once every two weeks. Of the 175 patients who completed ASCERTAIN, 168 continued into EXTEND: 37 from the sarilumab 150 mg group, 38 from the sarilumab 200 mg group and 93 from the tocilizumab group [21]. The primary outcome measure in the EXTEND trial was the number of treatment-emergent adverse events (TEAEs), and secondary outcome measures included ACR20 response, Disease Activity Score (28 joints) (DAS28)-C-reactive protein (CRP), and European League Against Rheumatism (EULAR) response. Improvements observed in DAS28-CRP in ASCERTAIN were maintained after the switch to open-label sarilumab in EXTEND through Week 60 and were also seen in patients who were non-responders on entry in EXTEND. Generally, the proportion of non-responders who achieved a response with sarilumab 200 mg was greater in the group that switched from tocilizumab or sarilumab 150 mg than in the group that was maintained on sarilumab 200 mg. Although based on a limited population, according to the authors these findings suggest that switching tocilizumab non-responders to sarilumab may have favorable efficacy outcomes.

Another post hoc analysis of the MOBILITY and TARGET trial documented the high efficacy of the IL-6 blocker sarilumab [22]. In this analysis, the proportion of patients who achieved treat-to-target goals of remission or low diseases activity (LDA) by 1 year in MOBILITY and 6 months in TARGET was assessed. Although remission and LDA generally became evident after four to eight weeks in most patient groups, with ongoing sarilumab treatment additional patients achieved remission and LDA at each successive time point assessed through week 24 in both studies (Figure 3). Some further increases were observed up to week 52 in MOBILITY.

Methotrexate drug holiday improves flu vaccine efficacy

Patients with immune-mediated inflammatory diseases such as RA are at increased risk of vaccine-preventable disease due to the fact that the immune response in these patients may be subdued [23]. Hence, for this patient population the benefits of implementing a suitable vaccination protocol in daily clinical practice are potentially even greater than for the general population. Despite this fact, vaccination coverage rates of RA patients rarely exceed those in the general population [24]. Efficacy of vaccines can be compromised by immune suppressive therapy: Methotrexate (MTX) has been shown to reduce efficacy of influenza vaccine, although RA patients taking MTX are at even higher risk of infection and infection-related complications [25] . A study presented during the meeting set out to investigate whether patients with RA could improve their response to influenza vaccinations by temporarily pausing methotrexate use for two weeks after their flu shot. "Our group has been working

on a novel immunization protocol for RA patients to optimize vaccine response, including increasing immunogenicity of flu vaccines," explained Prof. Jin Kyun Park, Seoul National University Hospital, Seoul (Korea) [26]. In this prospective, multicentre, randomized, parallel-group trial, 316 RA patients who were taking a stable MTX dose were randomly assigned to two groups: 156 continued their regular MTX and 160 discontinued their dose for two weeks after receiving their flu shot. All participants were vaccinated with a seasonal, quadrivalent influenza vaccine. 75.5% of the patients who temporarily discontinued their MTX dose achieved a satisfactory vaccine response, defined as the patients having a fourfold or greater increase in hemagglutination inhibition antibody titer at four weeks after vaccination against two or more vaccine strains compared to 54.5% of patients who continued their regular dosing. In addition, the seroprotection rate was higher for all four antigens measured in the group who held off methotrexate for two weeks than those who continued. The tolerability of the vaccine was good in all patients. Vaccination had no influence on disease activity in both groups. "The findings of this study have several potential clinical implications. First, we show a novel, effective, but simple way to improve vaccine response in RA patients who take MTX. Holding methotrexate for two weeks after vaccination improved vaccine response significantly without increasing disease activity. Therefore, patients should be advised to hold methotrexate for two weeks after vaccination," concluded Dr. Park. According to Dr. Park, this approach can probably also be applied to other vaccines, such as pneumonia or zoster.

Major depressive disorder (MDD): another risk factor for RA

"Recently, MDD has been identified to have a direct effect on cytokines, including increased serum concentrations of TNFα relative to healthy controls independent of underlying inflammatory disease", said Dr. Isabelle Vallerand, University of Calgary, Calgary (Canada) [27]. As prospective studies have shown that individuals with elevated TNFα are at increased risk of subsequently developing RA, they examined whether patients with confirmed MDD had a higher risk of RA than the general population without MDD.

The analysis from the Health Improvement Network (THIN) included a cohort of 403,932 patients with MDD and a general population cohort of 5,339,399 patients without MDD. Observation time was recorded for both the MDD and referent cohort until patients developed RA or were censored. Patients in the MDD cohort were more likely to be female, obese, and current smokers, and were more likely to have at least one comorbid disease and use antidepressants ($P< 0.0001$ for all). Patients with MDD had a 39% increased relative risk ($P< 0.0001$) of developing RA compared with the general population after adjusting for all covariates. The increased risk was attenuated when patients with MDD were treated with antidepressants targeting serotonin. "According to our results, prompt referral to a rheumatologist should be made when a patient with MDD presents with musculoskeletal symptoms characteristic of RA", recommended Dr. Vallerand. While the precise mechanism by which MDD contributes to this increased risk is unknown, future research should explore the possibility of adverse health behaviours and systemic inflammation as inciting factors, she added.

Digital coaching improves adherence

Not only medical therapy, but also lifestyle changes are essential to improve arthritis symptoms in RA. During the ACR meeting a trial performed by Pack Health, a digital health coaching company in Birmingham, Alabama was presented to examine the efficacy of a remote, behavior modification program for RA patients to help them reduce stressors related to their disease and make behavior changes [28]. "The hope was that when armed with the right information and tools and dedicated, one-on-one support on their schedule, participants would be able to improve key health behaviors as well as key measures of disease management and overall health," said Uma Srivastava, Associate Director, Strategic Partnerships at Pack Health in Birmingham. 127 patients with RA were enrolled in a 12-week digital health coaching program that included pairing each patient with a non-clinical health coach. Patients were contacted once a week by telephone, and these conversations centered on the principles of patient empowerment. To determine the impact of this telephone-based intervention, participants were surveyed about their behaviors and condition at baseline and after 12 weeks of coaching.

After 12 weeks, there was a decrease in body-mass index of 0.55 kg/m2, an increase in weekly physical activity of 76%, an increase in hours of sleep per night of 0.3 hours, and a 50% reduction in the number of medication doses missed each week. The physical as well as the mental health improved (assessed in the PROMIS Global Health-10 survey). Particularly impressive was a drop-in participants' RA flare frequency by 50% after program completion. The researchers concluded that this finding suggests symptom relief is associated with improvements in healthy behaviors and stressor reduction. "Often, patients with RA are overwhelmed,

and they require both coaching and care coordination to improve their well-being. However, rheumatologists often lack the time, tools and training required to effectively coach patients in the office environment," concluded Srivastava.

Reassuring news regarding biologic use during pregnancy

According to an observational study, infants of RA patients using a biologic during pregnancy do not have an elevated risk for infections [29]. Researchers included data on pregnant women in the U.S. or Canada, including those with and without RA, and those who used biologics and other therapies. The researchers collected data from the women in phone interviews, as well as from the medical records from the delivery hospitals and obstetric and specialty providers. Data included the dates when women started and stopped using biologics during their pregnancies. Information from 502 pregnancies where the mother with RA was treated with a biologic could be collected, and compared to 231 pregnancies of RA patients that did not use any biologics during pregnancy, and 423 pregnancies of healthy women. Follow-up data on infection rates of serious and/or opportunistic infections including neonatal sepsis, invasive fungal infection, X-ray proven pneumonia, meningitis, bacteremia, pneumocystis, septic arthritis, osteomyelitis, tuberculosis, herpes, listeria, legionella, mycobacteria, systemic cytomegalovirus and abscess in the infants were collected from their pediatricians for up to one year after birth. Serious or opportunistic infections occurred in 4.0% of the infants born to mothers with RA that used biologics during pregnancy. However, serious or opportunistic infections occurred also in 2.6% of the infants who were born to mothers with RA who did not use biologics and in 2.1% of the infants born to healthy mothers. The infection rates among infants potentially exposed in the third trimester is critical, because most experts believe placental transfer of biologics is increased in the late pregnancy. But even infants of women with RA whose last biologic dose was after 32 weeks of gestation had approximately the same risk of infections like infants of mothers with RA who did not use any biologic during pregnancy.

"These results should be reassuring for women with RA who need to be treated throughout pregnancy with a biologic," said Prof. Christina Chambers, Co-Director of the Centre for Better Beginnings, University of California, San Diego (USA). "This is true especially with later pregnancy exposure, when placental transfer is increased."

Age and low CRP predict success in tapering of biologics

RA patients who are in sustained remission often may taper their biologic dose. But are there predictors of successful tapering? This question was addressed by a Japanese trial presented during the meeting [30]. The authors analyzed a retrospective cross-section of RA patients to look for predictive factors that led to successful down-titration, or determining the most effective lower dose, of biologic DMARDs. In the study, 347 RA patients from two university hospitals in Japan were enrolled. They included patients who fulfilled the 1987 ACR and/or 2010 ACR/EULAR classification criteria and were treated with any one of the following biologics for longer than six months: infliximab, adalimumab, etanercept, golimumab, certolizumab-pegol, tocilizumab or abatacept. Patients enrolled in this study had a mean age of 62.5 years, mean disease duration of 12.3 years and were predominantly female (83.6 percent). Patients were divided into two groups, where 255 patients were on a stable treatment and 92 patients were tapered.

The two groups were similar with regard to their baseline disease activity, as defined by different disease activity scores, the prevalence of anti-citrullinated protein antibody and rheumatoid factor and X-ray findings. However, several significant differences were observed. Successful taperers were both younger at disease onset (mean age of 47.1 vs. 51 in stable treatment group) and at the time they began using biologics (mean age of 55.5 vs. 59.6 in stable treatment group). In addition, tapering was more successful in biologic--DMARD naïve patients (74% compared to 56%). Another patient characteristics associated with positive tapering was no concomitant use of oral corticosteroids and low CRP levels. "An important strength is that this study reflects the 'real world' experience," said Dr. Takaaki Komiya, Yokohama City University Graduate School of Medicine, Yokohama (Japan).

"The results of this preliminary study may help rheumatologists to differentiate RA patients who would successfully down-titrate biologics. This management might result in substantial reduction in costs and possible reduction in dose-dependent side effects," concluded Dr. Takaaki.

Opioid/antidepressant use correlates with higher fracture risk

Researchers at the University of Nebraska Medical Centre in Omaha and the National Data Bank for Rheumatic Diseases in Wichita, Kansas, conducted a study to look at associations

of various medications commonly used by RA patients with osteoporotic fracture risk [31].

Many RA patients have several comorbidities and are forced to use multiple medications. "Even at younger ages, RA is associated with a twofold increased risk of osteoporosis and fractures due to chronic inflammation and glucocorticoid use," said Dr. Gulsen Ozen, Research Fellow at the University of Nebraska Medical Centre in Omaha. Therefore, he studied factors associated with fracture risk, particularly modifiable ones, in RA patients in an observational cohort of RA patients form the USA. Medications that were included in the analysis were DMARDs, statins, antidepressants (including selective serotonin reuptake inhibitors (SSRIs) and others), proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants and antipsychotics. DMARDs were categorized into four groups: methotrexate monotherapy (comparator group), TNF-inhibitors, non-TNF biologics and others, along with a separate glucocorticoid variable.

The study evaluated 11,049 RA patients 40 years of age or older that had not had a prior OP fracture from 2001-2016. During a median follow-up time of 5.7 years, the researchers found 863 osteoporotic fractures.

In general, patients who developed fractures were significantly older and had higher disease activity, longer disease duration, higher fracture risk and more comorbidity at baseline than those patients who did not experience fractures.

The risk elevation started after just one to 30 days of using opioids and after three or more months of using SSRIs or corticosteroids of any dose (Table 1). The authors hypothesize that the increased fracture risk linked to use of opioids or SSRIs may be due to an increased risk of falls associated with these medications.

"Knowing the risks associated with the use of these medications can guide rheumatologists and other physicians in choosing the most appropriate management strategies in patients, particularly the ones who have a high fracture or fall risk," concluded Dr. Ozen.

Metabolomics: a new way to improve rheumatoid arthritis treatment?

It is known for decades that cytokine production in RA is associated with altered energy metabolism and intake. Cytokines IL-1 beta and TNF-alpha cause cachexia and hyper metabolism in animal models [32]. "The musculoskeletal (MSK) system is metabolically very active using 30% body energy even when at rest", said Prof. Stephen Young, Institute of Inflammation and Ageing, University of Birmingham, Birmingham (Great Britain) [33]. Basal metabolic rate (BMR) is elevated in RA patients due to hyper catabolism caused by systemic inflammation. An elevated BMR is also related with worse disease outcomes in patients with RA. Current cigarette smoking further increases BMR in patient with RA and has a negative impact on patients self-reported functional status [34].

"Because metabolism is influenced by both our genes and our environment, it suggests that metabolism and metabolic changes may reflect not only an individual's set of genes, but also the disease processes going on in that individual," Dr. Young said. "Therefore, metabolomics can be a good way of looking at a summative assessment of an individual patient."

In a trial published 2013, Prof. Young could show that urine metabolic profiles, assessed using nuclear magnetic resonance spectroscopy were able to predict patients' response to anti-TNF therapy [35]. "Metabolic profiling therefore may allow development of novel approaches to optimize therapy" said Prof. Young. In addition, metabolic profiles from the serum allow a prediction about the future course of the disease. "We've taken serum from RA patients, mainly in early disease when they've only had their joint symptoms for a matter of weeks or a few months, and have been able to make a prediction about whether they're going to develop chronic RA or have a self-limiting disease," Prof. Young said. According to his research, a number of metabolic pathways may be useful in suggesting novel therapeutic targets that allow to provide personalized medicine in RA patients.

Table1: Adjusted HR for fracture risk associated with medications for in RA patients.

	Incidence rates (95% CI) Per 1000 patient-years	Adjusted HR (95% CI)
All patients	16.5 (15.4-17.6)	
Glucocorticoid use		
< 7.5mg/d for <3 months	13.8 (7.2-26.5)	1.01 (0.45-2.26)
<7.5mg/d for ≥3 months	21.6 (18.9-24.7)	1.27 (1.06-1.53)*
≥7.5mg/d for <3 months	24.3 (14.7-40.3)	1.57 (0.84-2.95)
≥7.5mg/d for ≥3 months	34.1 (28.4-40.9)	1.74 (1.37-2.22)*
Antidepressants		
SSRIs	26.3 (22.6-30.5)	1.35 (1.10-1.64)*
Others	22.4 (17.9-28.1)	1.04 (0.80-1.36)
Opioids		
Weak opioids	26.3 (23.5-29.4)	1.48 (1.26-1.74)*
Strong opioids	40.4 (33.4-48.8)	1.78 (1.41-2.26)*

* P<0.05 HR = hazard ratio, CI = confidence interval. [18]

CRIB and CRADLE: reassuring results for pregnant and lactating patients with CID

Many patients with chronic inflammatory diseases (CID) are of child bearing age and require continuous treatment. The CRIB and CRADLE trials assessed placental transfer and transfer through breastmilk of certolizumab pegol in this sensitive patient group.

Virtually no placental transfer in the CRIB trial

The CRIB trial was designed to measure the potential level of placental transfer of certolizumab pegol (CZP) from pregnant women to their infants [36]. Sixteen women (≥ 30 weeks gestation) who were already receiving CZP for approved indications (RA, Crohn´s disease, PsA and axSpA/AS) were followed in the study. Blood samples were collected from each woman, the umbilical cords, and their infants at delivery and again from infants at weeks four and eight post-delivery. CZP blood concentration was measured with a sensitive, specific electro chemiluminescence immunoassay with a lower level of quantification (LLOQ) of 0.032 µg/ml, which is 10 times more sensitive than prior assays for this agent. The study found that CZP levels were below LLOQ in 13 out of 14 infant blood samples at birth, and in all samples at weeks four and eight. One infant had a minimal CZP level of 0.042 µg/ml.

"The CRIB study is the only clinical research that demonstrates how an effective anti-TNF, certolizumab pegol, shows minimal to no placental transfer from mother to infant. This is very encouraging news for female patients who have an active inflammatory disease, and require treatment during pregnancy," concluded first study author Prof. Xavier Mariette, Head of Rheumatology, Bicetre Hospital, Paris-Sud University, Paris (France).

Also, compatible with breastfeeding

The CRADLE study was performed to determine the concentration of CZP in human breast milk of lactating mothers (≥6 weeks postpartum) receiving CZP for an approved indication at day 0,2,4,6,8,10,12, and 14 of [37]. Using the highly sensitive assay, the agent was undetectable in 56% of milk samples. When detectable, CZP concentrations were < 1% of expected plasma concentration of a therapeutic dose, indicating no to minimal transfer of CZP from plasma to breast. Relative infant dose was below 0.5% of maternal dose; <10% is considered unlikely to be of clinical concern. In addition, CZP absorption by infants via breast milk is unlikely due to CZPs Fc-free molecular structure and the low bioavailability of biologics after oral administration. The authors therefore conclude that continuation of CZP treatment is compatible with breastfeeding.

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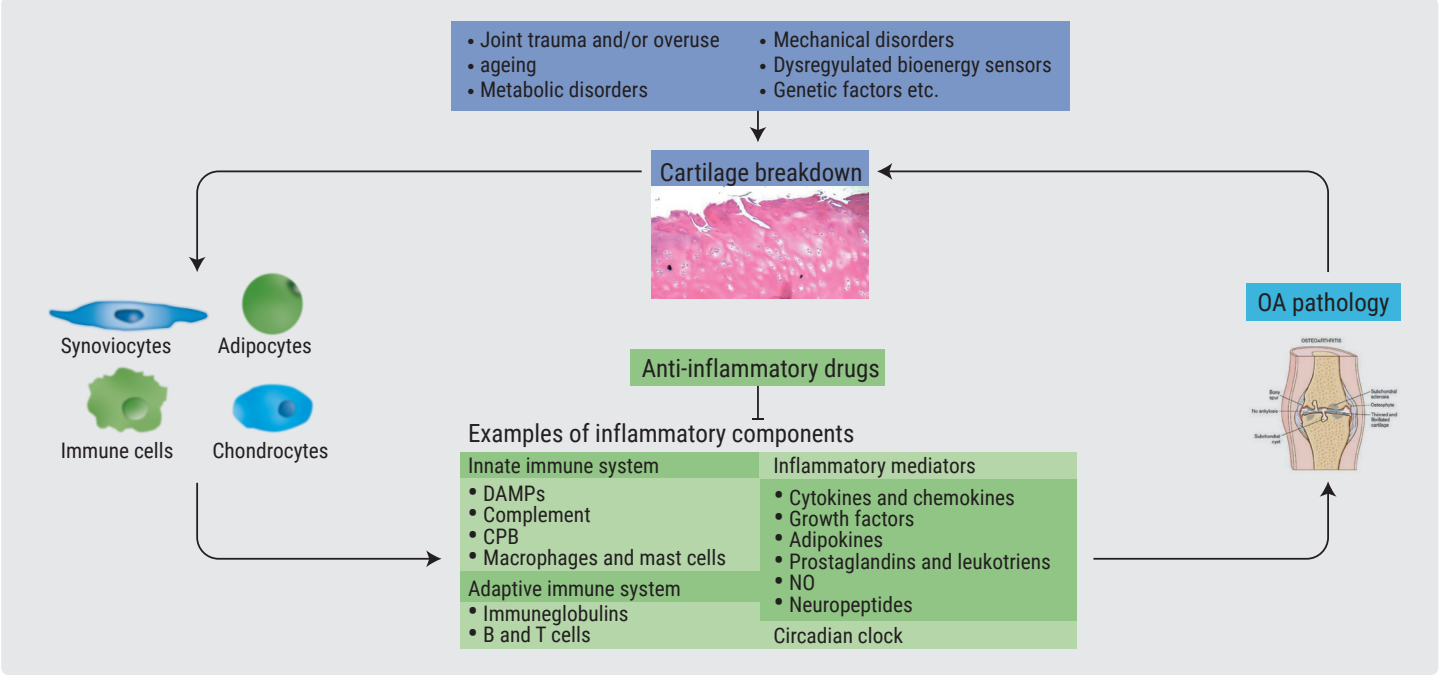
Inflammation: A Key Factor in Pathogenesis of Osteoarthritis

Osteoarthritis (OA) is no longer seen as a degenerative disease. Low grade chronic inflammatory processes lead to the destruction of the cartilage.

Osteoarthritis: far more than a "wear and tear" process

In the past, OA was regarded as a solely degenerative disease. However, the pathogenesis of OA is much more complex. The new paradigm of OA as a chronic low-grade inflammatory disease began with the detection of the catabolins, a low molecular weight peptide that subsequently was named Interleukin (IL)-1, which is released by synovial tissue. IL-1, IL-6 and TNF alpha play a key role in its pathogenesis. "Altered biomechanics promote inflammation" explained Prof. Steven B. Abramson, NYU School of Medicine, New York (USA) [1]. The OA group consists of two distinct populations, the fast progressors and the non-progressors. Only 10 to 20% of all OA patients are rapidly progressing. Therefore, it is of key importance to find biomarkers that predict progression. Patients with symptomatic OA often have high prostaglandin (PG) E2 and high C reactive protein (CRP) levels. "Unfortunately, as the majority of our patients is overweight, it is hard to tell whether elevated CRP levels derive from obesity or OA", said Prof. Abramson. Another pro- and anti-inflammatory mediator that are produced by joint tissues in OA and might contribute to pathogenesis are IL-1ß and IL1Ra. In a trial in 111 patients with symptomatic knee OA, Plasma levels of IL1Ra were modestly associated with the severity and progression of the disease, in a causal fashion, independent of other risk factors [2]. "Patients with more than 3fold elevation of IL1Ra had higher levels of pain, assessed in the WOMAC total score. "The more inflamed the tissue is, the more pain you have", explained Prof. Abramson. In a 24-month prospective study including patients with symptomatic knee OA, inflammatory plasma lipid biomarkers PGE2 and 15-HETE identified patients with symptomatic knee OA [3]. In the 146 patients who completed the 24-month study, elevated baseline expression of IL-1β, tumour necrosis factor α, and cyclooxygenase 2 (COX-2) messenger RNA in plasma and peripheral blood leukocytes predicted higher

Figure 1 Targeting low grade inflammation in OA. CPB, carboxypeptidase B; DAMPs, disease-associated molecular patterns; NO, nitric oxide; OA, osteoarthritis. [5]



risk of radiographic progression as evidenced by joint space narrowing (JSN). Another trial showed that soluble receptors for TNF-alpha, are present in the synovial fluid of patients with primary knee osteoarthritis, further backing the thesis that inflammation plays a critical role in its pathogenesis [4].
OA pathogenesis involves not only breakdown of cartilage, but also remodeling of the underlying bone, formation of ectopic bone, hypertrophy of the joint capsule, and inflammation of the synovial lining [5]. OA is a disorder of the joint as a whole. The inflammation in OA is distinct from that in rheumatoid arthritis and other autoimmune diseases: it is chronic, comparatively low-grade, and mediated primarily by the innate immune system (Figure 1).

Crystals contribute to progression in knee OA

"If you have chondrocalcinosis, this will double your risk of progression", said Prof. Abramson. This showed a study published earlier this year [6]. In this trial was investigated whether serum uric acid (UA) levels predict OA progression in a non-gout knee OA population. OA progression was assessed by JSN from 0-24 months. In this trial, serum UA levels correlated with JSN. "The risk of JSN was high when you came to the solubility point of UA of 6.8mg/dl" said Abramson. Baseline serum UA levels distinguished progressors (JSN>0.2 mm) and fast progressors (JSN >0.5 mm) from non progressors (JSN ≤0.0 mm) in multivariate analyses in this trial. Therefore, the authors conclude that in non-gout patients with knee OA, the serum UA level predicted future JSN and may serve as a biomarker for OA progression. Earlier trials implicated already that synovial fluid UA is a potential OA biomarker, possibly reflecting chondrocyte damage.

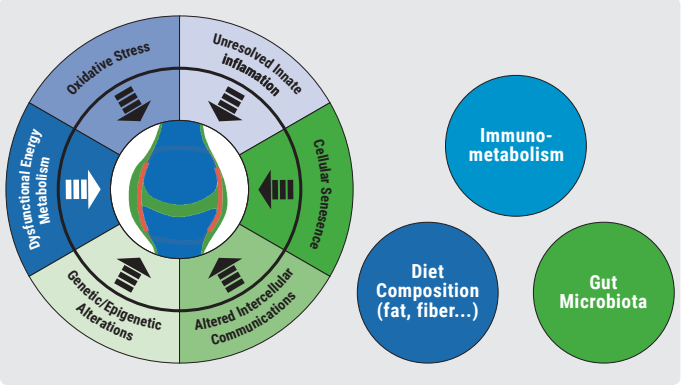
Obesity: a key driver of low grade inflammation

"We know that obesity is a major risk factor for osteoarthritis and there are some compelling new findings emerging on how some metabolic factors, such as inflammation associated with adipose tissue, are altered in osteoarthritic conditions and may be involved in the progression of osteoarthritis," said Prof. Timothy Griffin, University of Oklahoma Health Sciences Centre in Oklahoma City (USA) [7]. In an experimental model, he and his team induced OA in mice by a very high-fat diet [8]. In addition, levels of serum leptin, adiponectin, and IL-1 receptor antagonist to an extent in proportion to the gain in body fat (3-fold increase in percent body fat compared to controls) where increased. Wheel-running exercise reduced progression of OA in the medial femur of obese mice. The authors conclude that obesity causes OA and systemic inflammation in proportion to body fat. Exercise improves glucose tolerance and disrupts the co expression of proinflammatory cytokines, suggesting that increased aerobic exercise may act independently of weight loss in promoting joint health. Even if the precise metabolic pathways through which obesity contributes to joint structural damage are currently not known, elevated oxidative stress, altered intercellular communication, unresolved innate inflammation, and dysfunctional energy metabolism contribute to the deleterious effect of obesity on OA (Figure 2). In addition, there are genetic biomarkers: Polymorphism of the IL-1RA gene are associated with early onset knee OA.
By understanding the mechanisms driving joint tissue destruction in OA, hopefully new targets for therapy are emerging that might be able to halt the progression of OA.

Intra-articular corticosteroids: friend or foe

Intraarticular corticosteroids (IACS) are widely used for OA knee pain, although there are longstanding concerns about accelerated damage. In a two-year RCT the potential for disease modification of OA among knees with synovitis by IACS was performed [9]. In this trial, primary outcome assessments were cartilage volume loss as well as a clinical outcome like scores in the pain domain of the WOMAC. Two years of intraarticular (IA) triamcinolone, compared with intraarticular saline, resulted in significantly greater cartilage volume loss and no significant difference in knee pain. These finding do not support this treatment for patients with symptomatic knee OA.
According to a network meta-analysis of OA treatments that allows to compare relative effects of all treatments against each other, intra-articular treatments were superior to NSAIDs (acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib), possibly because of the integrated IA placebo

Figure 2 Adiposity contributes in many ways to the progression of OA. [7]



effect [10]. Small differences were observed between active treatments. For pain, IA hyaluronic acid injections were most efficacious. All treatments except acetaminophen showed clinically significant improvement from baseline pain. Regarding function of treatments, all interventions except IA corticosteroids were significantly superior to oral placebo. "Another extended release formulation of triamcinolone acetonide (Fx006) for IA injection yielded better results in a trial", said Prof. Timothy McAlindon, Tufts Medical Centre, Boston (USA) [11]. In this trial, treatment with FX006 provided statistically and clinically significant, sustained improvements in pain/stiffness/function of knee OA vs placebo [12] and got an FDA approval in October. An abstract presented during this meeting showed that FX006 is effective irrespective of baseline clinical inflammation, determined by clinical assessment [13].

Gaps in the non-surgical management

During this year's ARHP Distinguished Lecture, Dr. Kelli D. Allen, University of North Carolina, Durham VA Medical Centre, Durham (NC/USA), emphasized that although different OA guidelines are in agreement with each other and based on systematic reviews of research findings, there is a lack of sufficient evidence for many treatments, and the guidelines remain silent on key issues such as sleep, social determinants, comorbidities, and psychological factors [13]. "Studies showed that only 52% of patients reported that a healthcare provider recommended physical activity. While 80% of OA patients are overweight or obese, only four out of 10 patients reported that a healthcare provider had provided recommendations for weight management", said Dr. Allen.

Another study found that 90% of knee OA patients who had joint replacement surgery in the United States never received physical therapy in the five years prior to surgery.

"The general picture that I take away from this is that we have some gaps to fill, particularly when it comes to a whole range of non-surgical treatments for OA," Dr. Allen said.

Pain relief and functional improvement in knee OA: thanks to oral supplement

An oral supplement with the ingredient chondroitin sulfate provided superior pre-defined levels of pain relief and/or functional improvement as compared to those receiving placebo in patients with symptomatic knee osteoarthritis (OA) [14]. The differences in responder rates were both statistically significant and clinically relevant. This showed a study data from the Chondroitin vs. Celecoxib vs. Placebo Trial (CONCEPT). presented by Prof. Jean-Yves Reginster, Liege State University, Liege (Belgium). In this trial, the following responder definitions were used: pain reduction of 30% vs baseline (moderate pain relief), pain reduction of 40% vs. baseline (moderate-to-substantial pain relief), pain reduction of 50% vs. baseline (substantial pain relief).

The analysis included 404 of the 604 patients enrolled in the CONCEPT study, who were age older than 50 years and had knee OA of the medial or lateral compartment diagnosed according to the clinical and radiographic criteria of the ACR. Of these patients, 199 were treated with chondroitin sulfate 800 mg/d and 205 with placebo. The remaining 200 patients in the control group with active treatment (celecoxib 200 mg/d) were excluded. The responder rates for pain reduction were consistently higher in the chondroitin sulfate group than in the placebo group at each pre-determined level of pain reduction. The rates were 69% and 61% in the chondroitin sulfate and the placebo group, respectively, for a pain reduction of 30% vs. baseline, 64% and 52% for a pain reduction of 40% vs. baseline, and 58% and 40% for a pain reduction of 50 % vs. baseline.

The study also found comparable results for the Lequesne Index (LI). The rates were 56% and 45%, respectively, for the chondroitin sulfate and placebo groups, for an LI reduction of 30% vs. baseline, 47% and 35%, respectively, for an LI reduction of 40% vs. baseline, and 37% and 27% for an LI reduction of 50% vs. baseline. According to the Outcome Measures in Rheumatology-Osteoarthritis Research Society International criteria, 66% and 55% of patients in the chondroitin sulfate and placebo groups, respectively, were found to be responders after 6 months of treatment (P=0.021). "Given the compelling benefit-risk profile coupled with the known clinical risks associated with chronic usage of non-steroidal anti-inflammatory drugs and paracetamol, the results show the potential importance of chondroitin sulfate in the management of knee OS, particularly in this older population requiring long-term treatment," concluded Prof. Reginster.

Opioid use not recommendable in osteoarthritis patients

A significant percentage of patients with end-stage knee, hip and spine osteoarthritis use opioids to manage their chronic pain, especially those who are younger or have symptoms of depression: This showed a Canadian study including 1,204 pre-surgical patients with knee, hip and spine OA [15].

"Growing evidence demonstrates little if any clinically significant benefit of opioids for OA pain, particularly when compared to other medications. There are growing concerns about the potential for misuse, dependency and increased adverse events, including opioid-related death," said Prof. Y.

Raja Rampersaud, University of Toronto in the Divisions of Orthopaedic and Neurosurgery (Canada).

The study participants included 577 patients with knee OA, 459 patients with hip OA and 168 patients with spine OA. All were scheduled for surgery at a tertiary care hospital in Toronto. The study participants were of a mean age of 65.6 years and 55.5 percent were women. Participants were given pre-surgery questionnaires to collect data on their opioid usage. They were asked if they used opioids for pain never, sometimes or daily. They were also asked if they used other medications for arthritis or joint pain, such as NSAIDs, antidepressants or neuroleptics, and over-the-counter medications. Overall 15% of patients reported that they sometimes used opioids and an additional 15% reported daily use of these medications. Reported opioid use was highest among the spine OA patients at 40% and similar among knee and hip OA patients at 28 and 30%, respectively. Greater likelihood to use opioids was significantly associated with spine OA, younger age, obesity, the presence of fibromyalgia along with OA, greater depressive symptoms, greater pain and the current use of other prescription pain medications. The researchers concluded higher use of opioids among younger patients and those with greater depressive symptoms is especially concerning due to the possibility of opioid-related adverse effects.

"We found that those with the highest use also reported the highest levels of pain, suggesting that perhaps the opioids were not having their intended pain-reducing effect on all patients" said Prof. Rampersaud. Given the relative lack of efficacy, OA patients should not be started on opioids to begin with, and if necessary, only for short durations at the lowest possible dose. "Our findings demonstrated that pre-surgical opioid use is an independent predictor of a greater degree of pain at three months post-surgery", concluded Prof. Rampersaud.

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Systemic Lupus Erythematosus: Lifestyle Factors are of Key Importance

During the meeting, new data shed light on the pathogenesis and progression of lupus nephritis. In addition to medical therapy, systemic lupus erythematosus (SLE) patients may benefit in many ways from nutrition counseling.

Renal involvement: a key mortality predictor in SLE

Varying degrees of renal involvement are seen in up to 60% of adults with SLE, and severe lupus nephritis (LN) (World Health Organization class III and above) progresses to end-stage kidney disease within 15 years of diagnosis in 10% to 30% of patients [1]. Renal injury is also the most important predictor of mortality in patients with SLE [1]. During the meeting, several studies addressed renal disease in SLE. The microbiome is an important factor contributing to lupus nephritis. "Our intestines are home to 1010-1014 microbial cells, three times more than the number of host cells", said Prof. Gregg J. Silverman, New York University School of Medicine, New York (USA) [2]. The gut microbiome plays an important role in priming and maintenance of the human immune system. Imbalances in gut microbiome are linked to the pathogenesis of many diseases, e.g. inflammatory bowel

disease, type 1 diabetes, asthma, atopic eczema, multiple sclerosis and RA. The contribution of the intestinal microbiome to immune abnormalities in active SLE is yet unexplored. Prof. Silverman and his team therefore characterized gut microbiota in SLE, with special interest in Lupus nephritis. In a cross-sectional study of 61 SLE patients, blood and fecal samples were obtained and 16S rDNA next generation sequencing was performed. Two independent lupus cohorts were studied for validation.

In general, patients with higher disease activity (assessed in the SLEDAI) had less diversity in their microbiome (Figure 1). The microbiota of patients in clinical remission (based on SLEDAI) were most similar to healthy controls, while reductions in taxonomic complexity were most pronounced in those with high disease activity. "If patients get sicker and sicker, we find increasingly less and less species", said Prof. Silverman.

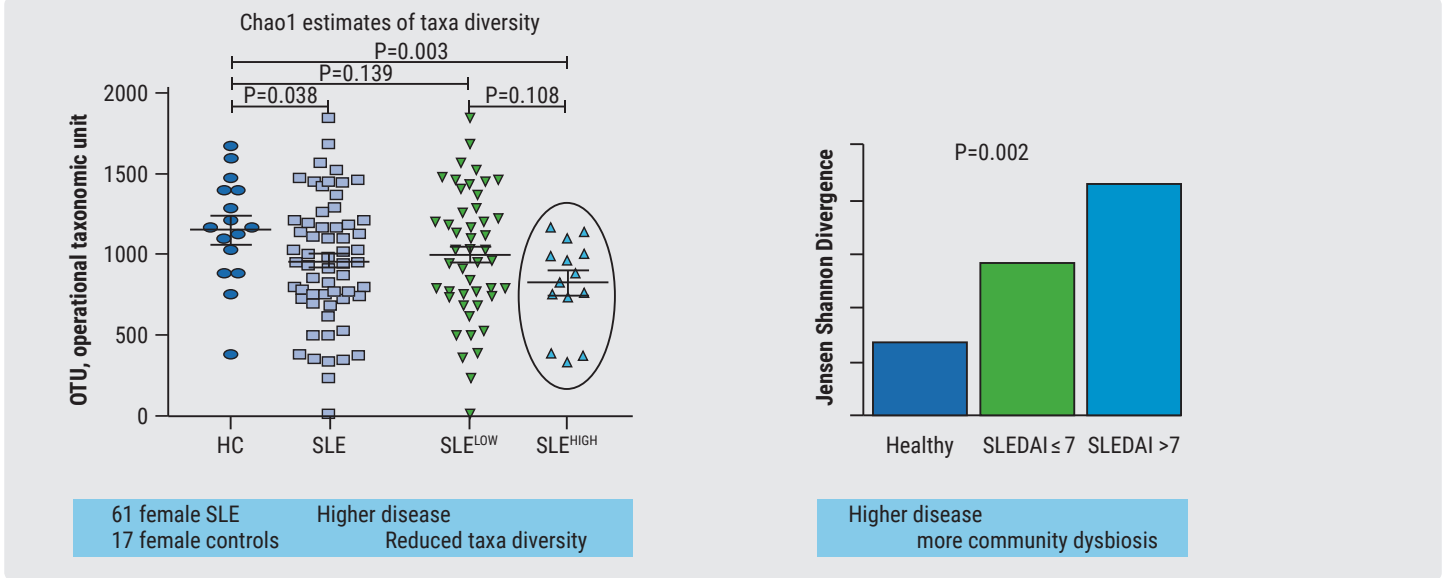
In addition, SLE patients had overall a more than 5-fold increase in Ruminococcus gnavus abundance, a species belonging to the lachnospiraceae family. High disease activity was associated with even greater R. gnavus outgrowth. Higher SLE disease activity correlated with higher serum IgG anti-R. gnavus levels. High IgG anti-RG2 levels identified patients with active LN (ACR criteria and biopsy) in three independent cohorts. As Prof. Silverman pointed out, these findings suggest a novel paradigm for the pathogenesis of LN, in which specific strains of common intestinal commensal bacteria contribute to the immune-complex mediated disease process responsible for glomerulonephritis. This is reminiscent of poststreptococcal glomerulonephritis, although in LN the postulated intestinal bacterial dysbioses and microbial expansion appear to occur without outward signs and symptoms of clinical infection.

Low vitamin D concentrations dangerous for SLE patients

A study presented by Dr. Michelle A. Petri and her colleagues of the "Hopkins Lupus Centre" at Johns Hopkins University School of Medicine in Baltimore (USA) showed that low levels of vitamin D are associated with higher rates of end-stage renal disease in patients with SLE [3].

SLE patients have low serum levels of vitamin D, which increase the possibility of an association between vitamin deficiency and disease onset and evolution. To clarify the role vitamin D levels may play in lupus inflammation, Dr. Petri and coworkers conducted a study to determine how low vitamin D levels could predict later organ damage. The researchers analyzed data on 1,392 SLE patients, including their first visit where vitamin D levels were measured, and then their organ or tissue damage on all of the patient's follow-up clinic visits. The patients included in this study were 92% female, had a mean age of 47.3 years, and were 50% Caucasian and 41% African-American. The risk of lifetime organ damage for patients with low vitamin D levels was calculated using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index scoring system. SLE patients whose vitamin D levels were insufficient (below 20ng/ml) had an 87% elevated risk (66% adjusted) to develop end stage renal disease. Skin damage was another concern, with a 69% higher risk (22% adjusted). Even total organ

Figure 1 In SLE, reduced microbiome diversity is associated with higher disease activity. [2]



damage relative risk was elevated by 11% (17% adjusted).
"Previously we have shown that supplementing vitamin D reduces urine protein, which is the best predictor of future renal failure," said Dr. Petri. "Supplementary vitamin D helps to prevent one of the most dreaded complications of SLE. Vitamin D supplementation, which can reduce proteinuria, should be a part of the treatment plan for lupus nephritis patients", concluded Dr. Petri.

Worse patient related outcomes in obese SLE patients

While obesity can worsen systemic inflammation in the general population and contributes to worse disease-related outcomes in RA, its impact in lupus patients is not well established [4]. New data presented during the meeting showed that obesity is also independently associated with worse patient-reported outcomes in women with SLE, including disease activity, depressive symptoms, pain and fatigue [5]. Study participants had to be at least 18 years old, female and have a diagnosis of SLE verified by medical record review. In addition to body Mass Index (BMI), fat mass index (FMI), a measure of total fat mass adjusted for height, was calculated from whole dual X-ray absorptiometry (DXA) assessments. FMI greater than or equal to 13 kg/m2 and BMI greater than or equal to 30 kg/m2 was defined as obese. The association of obesity with four patient-reported outcomes, disease activity measured according to the Systemic Lupus Activity Questionnaire (SLAQ), depressive symptoms according to the Centre for Epidemiologic Studies Depression Scale (CES-D), pain using the Short Form 36 Health Survey (SF-36) Pain Subscale, and fatigue using the SF-36 Vitality Subscale were evaluated and controlled for potential confounders (e.g. age, race education, glucocorticoid use).
Nearly a third of patients were obese, confirming the fact that obesity is a common comorbidity for people with SLE (32% according to the FMI definition of obesity and 30% according to the BMI definition). Using a multivariate regression model, obesity as defined by FMI was associated with worse scores for each patient reported outcome: greater disease activity, higher levels of depressive symptoms, more pain and more fatigue. The researchers found the same relationship between obesity and these four outcomes after repeating the analyses using the BMI cut-off point for obesity. "Our findings have important clinical implications because particularly pain and fatigue are known to have profound effects on quality of life and remain a major area of unmet need for people with lupus," said Dr. Sarah Patterson, a fellow in rheumatology at the University of California, San Francisco. "The relationship we observed between excess fat and worse outcomes underscores the need for lifestyle interventions targeting lupus patients who are overweight". Such interventions will address both cardiovascular risk and the severity of debilitating symptoms.

Nutrition counseling can also improve quality of sleep in SLE patients

"In the past, small studies showed an association between omega-3 supplementation and reduced disease activity in lupus patients, but no studies have looked at omega-3 exposure through diet or its impact on patient reported outcomes," said Prae Charoenwoodhipong, student in the Department of Nutrition Science at the University of Michigan School of Public Health in Ann Arbor (USA) [6-7]. Omega-3 fatty acids generally exert an anti-inflammatory and omega-6 fatty acids a pro-inflammatory effect. Western diets are often much higher in the proinflammatory omega-6 fatty acids. To assess the influence of nutrition on patient reported outcomes in SLE, a population-based, cross-sectional study using data from the Michigan Lupus Epidemiology & Surveillance (MILES) program was started. Data on dietary intake of omega fatty acids at baseline were collected using questions from the National Cancer Institute's Diet History Questionnaire. Patient-reported outcome data included the Systemic Lupus Activity Questionnaire (SLAQ), RAND 36 Healthy Survey, Fibromyalgia (FM) Scale, PROMIS Sleep Disturbance (short form 8b) and PROMIS Depression. Covariates like age, sex, race, energy intake and BMI were adjusted in the analysis.
456 out of 462 SLE patients enrolled in the program completed the dietary questionnaires at baseline. After controlling for covariates, researchers found that increasing omega-6 to omega-3 ratios in the diet were associated with SLE disease activity. Intake of the anti-inflammatory omega-3 fatty acids was significantly associated with better sleep quality and trended toward significant decreases in depressive symptoms and the presence of comorbid fibromyalgia. There was no influence of diet on general health-related quality of life. "Many SLE patients suffer from symptoms such as poor sleep, fatigue and depression," said Charoenwoodhipong.
"Recommending daily servings of fatty fish, nuts and seeds that are rich in omega-3 fatty acids and avoiding a lot of foods that are high in omega-6 could be a low-toxicity intervention that is easily available for SLE patients and helps to address these symptoms". Future studies should investigate whether omega-3-rich foods could help manage symptoms in lupus patients, as well as to identify other nutrients that may be beneficial, such as vitamins A, C or E.

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Autoimmunity and Cancer: A Close Liaison

More and more patients suffer from coexisting cancer and rheumatic disease. Oncologic comorbidity will be a challenge for rheumatologists in the future, as it may complicate therapeutic options.

Chronic inflammation links autoimmune disease and malignancy

Cancer and autoimmune diseases are closely connected. Rheumatic disease may be a marker of an underlying cancer, on the other hand, cancer may drive the development and propagation of the autoimmune disease. Newer cancer therapies have been shown to trigger rheumatic disease by inducing anti-tumour immune responses [1]. The relationship between cancer and autoimmune disease is mutual: Cytotoxic, biologic or immunotherapy prescribed for rheumatic disease can lead to secondary malignancies. Vice versa, if these agents are prescribed for cancer, they can trigger rheumatic disease. Another reason for the elevated cancer risk is the chronic inflammation and damage from the autoimmune disease. Patients with rheumatic disease might also be unable or more susceptible towards oncogenic infections.

Across the broad spectrum of autoimmune diseases, a marked risk elevation of cancer is seen in patients with myositis and scleroderma. "Data from scleroderma and myositis illustrate that natural occurring anti-tumour immune responses may lead to autoimmunity", says Prof. Ami Shah, Director of Clinical and Translational Research at the Johns Hopkins Scleroderma Centre, Baltimore (USA) [1]. Pooled analysis of published national data from Sweden, Denmark, and Finland showed that dermatomyositis is strongly associated with a wide range of cancers [2]. The overall risk of malignant disease was also modestly increased among patients with polymyositis. In both dermatomyositis and polymyositis, risk of malignant disease was highest at time of myositis diagnosis.

Recent data suggest a paraneoplastic mechanism of scleroderma pathogenesis in patients with scleroderma and RNA polymerase III autoantibodies [3]. "These patients really show us the link between cancer and autoimmunity", said Prof. Shah. "In our cohort of scleroderma patients, anti-RNA polymerase III positive patients had a more than 5-fold increased risk of cancer within two years of scleroderma onset", said Prof. Sha [4]. These findings were independently confirmed in Italy, the UK, Australia and Japan. In addition, older age at scleroderma onset and white race were significantly associated with an increased overall risk of cancer. In an analysis of 1,044 scleroderma patients, only anti-RNA polymerase III positivity and older age at scleroderma onset were significantly associated with a short cancer-scleroderma interval [5].

In some cases, autoimmunity may be initiated by autoantigen mutation in the patient's cancer [6]. However, there are patients with the same form of scleroderma and an identical autoimmune response who do not have a detectable cancer, raising the possibility that in these patients, the disease mechanism is the same except that the anti-tumour immune response has successfully eliminated the cancer.

Scleroderma: a by-product of anti-tumour response in a subset of patients

Genetic alterations in the gene encoding RNA polymerase III (POLR3A) have been identified, and patients with somatic mutations in POLR3A have evidence of mutation specific T cell immune responses with generation of cross-reactive RNA polymerase III autoantibodies. These data strongly suggest that scleroderma is a by-product of anti-tumour immune response in some patients: Transformation of normal cells to transformed cells may result in gene expression patterns that resemble immature cells. Occasionally, autoantigens become mutated. The first immune response is directed against the mutated form of the antigen, but then may spread to the wild-type version.

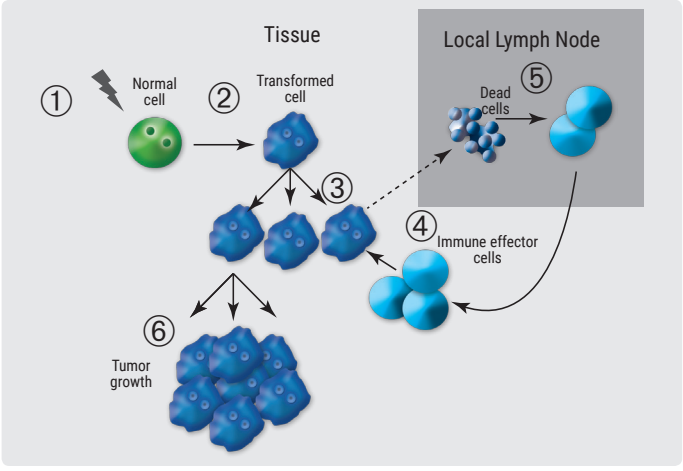
Immune effector cells then do not only delete cancer cells with or without the mutation, but also cross-react with the patient's own tissues (particularly immature cells expressing high levels of antigen, found in damaged/repairing tissue). Once autoimmunity has been initiated, the disease is self-propagating (Figure 1).

Anti-p155: a positive predictor of cancer in dermatomyositis

The autoantibody anti-p155 is a newly recognized autoantibody that is associated with dermatomyositis (DM) and cancer –associated dermatomyositis, as it is one of the most common autoantibodies in this condition [7]. A meta-analysis including six studies with 312 adult cases of dermatomyositis confirmed that this autoantibody is useful for diagnosing cancer associated myositis and guiding disease management [8]. In this analysis, 37 of 66 patients that were anti-p155 positive had cancer. Anti-p155 antibodies had a positive predictive value of 58% and a negative predictive value of 95% [9]. Other trials confirmed the importance of this antibody: In an English trial, 83% of patients with cancer –associated dermatomyositis could be identified by 2 autoantibodies, either anti-p155 or antiNXP2 [9].

Both in scleroderma and DM the increased risk of cancer is well established. In both conditions, there is a striking temporal relationship between cancer and rheumatic disease onset and particular autoantibody subsets are associated with cancer. In addition, disease-associated antigens are expressed in cancer tissue. At present, there are no evidence based recommendation for how to screen scleroderma or DM patients for cancer. However, cancer screening in DM should be intensified in patients that are anti-p155 or NXP2 positive.

Figure 1 Model for cancer-induced autoimmunity: when the immune response spreads to unmutated autoantigen, there is not only an anti-cancer effect, but also damage of tissues. [6]



"At least some of our autoimmune disease could be triggered by underlying cancers and the immune responses that develop in response to cancer", said Prof. Shah. Therefore, careful cancer screening may be appropriate, at least for patients with rheumatic disease and positive autoantibodies. However, there are no evidence based data to support that early diagnosis improves outcomes in these patients. On the other hand, if rheumatic diseases may be a manifestation of an underlying cancer, could cancer therapies be effective treatments for the rheumatic disease? There are many open questions of this liaison for future research.

What one should know about checkpoint inhibitors?

Immune checkpoint inhibitors (ICIs) are a new class of cancer immunotherapy that increased the survival in a variety of advanced malignancies. These agents are antibodies to programmed cell death-1 (PD-1), PD-1 ligand (PD-L1) receptors or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Many tumours express checkpoint ligands and dampen T-cell responses. ICIs work by blocking these negative costimulatory molecules, thus increasing activation of T cells, leading to an immune response directed against tumours.

Checkpoint inhibitors proved to be active in Malignant Melanoma, Merkel Cell Carcinoma but also urothelial carcinoma. "Many investigational agents with new targets are currently tested and there will be a continuously growing market for these agents", said Prof. Laura Cappelli, Johns Hopkins University School of Medicine in Baltimore [11]. Rheumatologists should care for both conceptual and practical reasons: tumours can express disease-defining autoantigens e.g. POLR3A. In addition, immune checkpoints like CTLA-4 or PD-1 are potentially important in SLE or RA.

Such nonspecific immunologic activation by ICIs can lead to immune-related adverse events (IRAEs). Some IRAEs, including inflammatory arthritis, sicca syndrome, myositis, and vasculitis, are of special interest to rheumatologists. They are seen in all agents and across all indications and can show diverse phenotypes (multiple organs and systems). Their severity ranges from mild to life-threatening. Risk factors of IRAEs are mostly unclear, but are more common during combination therapy with ICIs. Another problem is that musculoskeletal and rheumatic IRAEs are poorly recognized or described in RCTs, mainly because

the grading systems differ between oncologists and rheumatologists. According to the review of the literature, arthralgia and myalgia have been most commonly reported in patients taking ICIs: Arthralgia prevalence in clinical trials ranged from 1–43%, and myalgia was reported in 2–20% [12]. When immune checkpoint inhibitors have been used in patients with preexisting autoimmune disease, they can precipitate flare of the autoimmune disease in some patients. "We all need to be more familiar with the different autoimmune syndromes that can happen as a result of cancer immunotherapy and how we approach evaluating and managing these patients," Dr. Cappelli said. "We also need to consider the effects of checkpoint inhibitors in our patients with preexisting autoimmune disease and how we can work with oncologists to ensure that these patients have the best possible outcomes for both their cancer and their autoimmune disease." A cooperation between rheumatologist and oncologists is urgently needed.

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Fracture Prevention in Osteoporosis: Room for Improvement

Under treatment is a problem yet unsolved in current osteoporosis management. Drug holidays from bisphosphonates have been identified as a major reason for an increased fracture risk.

Vast under treatment, despite of effective medication

"There are about 200 million people with osteoporosis and about nine million fractures related to osteoporosis in the world every year, and despite the fact that we have excellent medications to reduce fracture risk and great tools to evaluate fracture risk to help us decide who needs to be treated, it's vastly undertreated virtually around the world", said Dr. E. Michael Lewiecki, New Mexico Clinical Research & Osteoporosis Centre, Albuquerque (USA), to outline the impact of the problem. In his talk, he pointed to the fact that there is a significant trend to a decline in prescription of osteoporosis medication [1]. Especially in older and male patient´s prescriptions are less likely and in general a great portion of patients are not treated in the year after their hip fracture [2]. According to Dr Lewiecki, this leads to a so called "treatment gap" of 80% and he advocates for setting a goal to reduce this gap to 20% within the next 10 years [1].

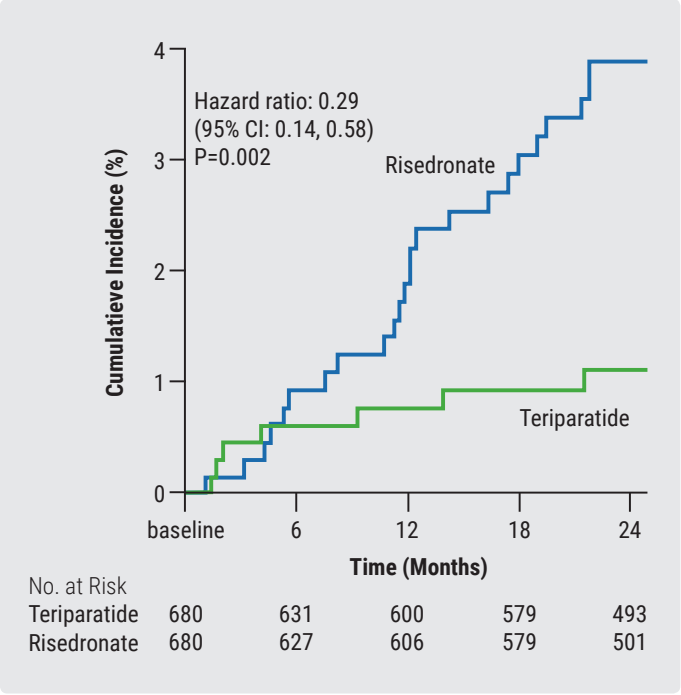
Drug holidays from bisphosphonates (BP) may be one of contributing factors to these low rates. They are increasingly practiced after 3-5 years of treatment, surely also in the light of FDA warnings about long-term risks [3]. In a study, Prof. Jeffrey C. Curtis, University of Alabama at Birmingham (USA), and his fellow researchers tried to elucidate the benefits and risks of stopping BPs, and the optimal timing to restart. Therefore, they conducted a cohort study from Medicare data. The investigation included 156,236 women who initiated a BP and were at least ≥ 80% adherent over at least 3 years, at which follow up time began. Mean age was 78.5, over 70% of them had used alendronate as BP. 40.1% of the women stopped taking BP for ≥ 6 months during the follow-up time of 2.1 years and among them 12.7% restarted medication afterwards. All in all, 3,745 hip fractures were diagnosed within study time and depending on the length of drug interruption the risk for hip fracture significantly increased between 12 % (>3 month ≤1 year) and 39% (>2 to ≤3 years). Hip fracture rates were lowest among women who were current users.

Treat-to-target concept to avoid fractures

Prof. Liewicki, also advocated for the so-called 'treat-to-target' concept that sets the therapy goal to achieving at least a T-score >-2.5 [1]. "Typically, when we treat for

osteoporosis, we'll start patients on the least-expensive drug that works fine for most people, such as generic alendronate", he explained the current practice. "In the past, we've generally been happy, if the patient responds to treatment and their bone density remains stable or goes up a little bit, but we shouldn't be satisfied if their risk of fracture still remains very high", Prof. Liewicki elaborated further. So, treat-to-target should be the aim for therapy of osteoporosis. Reaching this target, especially in patients with severe osteoporosis may include not only the choice of antiresorptive treatment with BP but also with anabolic agents like teriparatide. A new head-to head study compared the efficacy of this recombinant human parathyroid hormone (1-34) analog to that of risedronate in 1,360 postmenopausal women with ≥ 2 moderate or 1 severe vertebral fractures and a T-score ≤ -1.5 [4]. The participants of this 24-months, double-blind, double-dummy study had a mean age of 72.1 years. They were randomized to either 20µg/day of subcutaneous teriparatide or 35mg of oral risedronate per week. During the 2 years of follow-up, 1.1% of women in the teriparatide group experienced a clinical vertebral fracture with radiographic confirmation of a new or worsened vertebral fracture vs. 3.9% in the risedronate group, leading to a HR of 0.29 (Figure 1). Corresponding IR of events/patient-years were 0.58 and 1.97 for treatment with teriparatide and risedronate respectively. In conclusion, the researchers pointed out that teriparatide reduced the risk of a new clinical vertebral fracture by 71%.

Figure 1 Incidence of new clinical vertebral fractures during therapy with teriparatide compared to risedronate over 24 months. [4]



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Axial Spondyloarthritis Re-visited

There are many open questions regarding the management of patients with axial spondyloarthritis (axSpA), some of them could be answered with the help of new data presented during the meeting.

Patients with axSpA benefit from adalimumab continuation

"We know that TNF inhibitors should not be stopped in patients with ankylosing spondylitis, or radiographic axSpA," said Prof. Robert Landewé, Academic Medical Center, University of Amsterdam, Amsterdam (The Netherlands). But this was unclear in patients with non-radiographic axSPa [1]. The ABILITY-3 trial was designed to answer this question: 673 patients with active non-radiographic axSpA at baseline were enrolled and given open-label treatment with adalimumab for 28 weeks, after which time the 305 patients who achieved inactive disease according to an Ankylosing Spondylitis Disease Activity Score (ASDAS) below 1.3 points were randomly assigned to continue with adalimumab treatment (continuation) or switch to placebo (withdrawal) for an additional 40 weeks. 70% of patients who received continuous adalimumab treatment were free from flares at the 68-week follow-up, compared with 47% of those who switched to placebo (P<0.001). Patients continued with placebo had a 77% higher relative risk to experience a flare. In addition, all assessed secondary endpoints were in favor of continuation of adalimumab: a greater proportion

of participants who continued treatment achieved inactive disease (57% vs. 33%; P<0.001) or a major improvement in disease activity (59% vs. 32%; P<0.001) at week 68. Incidence of adverse events (AEs) among patients in the adalimumab and placebo groups were similar at week 68. A total of 1% of patients in the continuation group and 7% of those who switched to placebo experienced serious AEs. "The increased incidence of serious AEs among patients in the withdrawal group may be attributed to patients experiencing flares that led to hospital admission", concluded Prof. Landewé. According to the authors the results of the ABILITY-3 trial support the continuation of adalimumab therapy after achievement of sustained remission.

Higher disease activity in obese patients

It is well established that obesity is associated with a worse disease outcome in RA. However, there is little evidence about the effects of obesity on patients with axSpa [2]. An Irish study was performed to determine the prevalence of obesity in a large cohort of patients with axSpa and to examine whether obesity may be associated with worse disease outcomes. "Traditionally, we have a perception of patients with axSpa being of normal or even thin body build. However, recent studies have indicated that this is not the case, and that obesity is also prevalent in axSpa patients," said Dr. Gillian Fitzgerald, Rheumatology Specialist Registrar at St. James's Hospital in Dublin (Ireland). Data from a cohort from the Ankylosing Spondylitis Registry of Ireland (ASRI) were used in the analysis. 683 axSpa patients were enrolled in this study: 1.1% were underweight, 31.6% of normal weight, and a total of 67.3% overweight or obese. Patients with axSpa who were overweight or obese were significantly older, had the disease for a longer time, and more comorbidities. Obese axSpa patients also had significantly higher disease activity scores and worse physical function, spinal mobility and quality of life than patients who were either normal weight or overweight.

Pitfalls in axial spondyloarthritis diagnosis

MRI of the sacroiliac is a sensitive method for detection of bone marrow edema (BME) and structural lesions in axSpA. However, it may be misleading, when applied in healthy persons that undergo intensive physical activity: this showed a trial with 22 military recruits [3]. They were given MRI scans of their sacroiliac joints (MRI-SIJ) before and after six weeks of intense, uniform physical training. BME and structural lesions on the scans were scored by three trained readers. The recruits' results were also evaluated for agreement with the definition of a positive MRI per the Assessment of Spondyloarthritis (ASAS). At baseline, 40.9% of the recruits already presented with at least one BME lesion. At week six, this number increased to 50%. In the recruits who had BME, the mean number of lesions at baseline was 2.4, and rose to 3.7 at week six. In addition, 22.7% of recruits had a positive MRI according to the ASAS definition, and this increased to 36.4% at the follow-up. "Our study does show the importance of the necessary caution when interpreting MR images of the sacroiliac joint of physically active people. A wrong diagnosis of SpA is easily made," concluded Thomas Renson, Ghent University, Ghent (Belgium).

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