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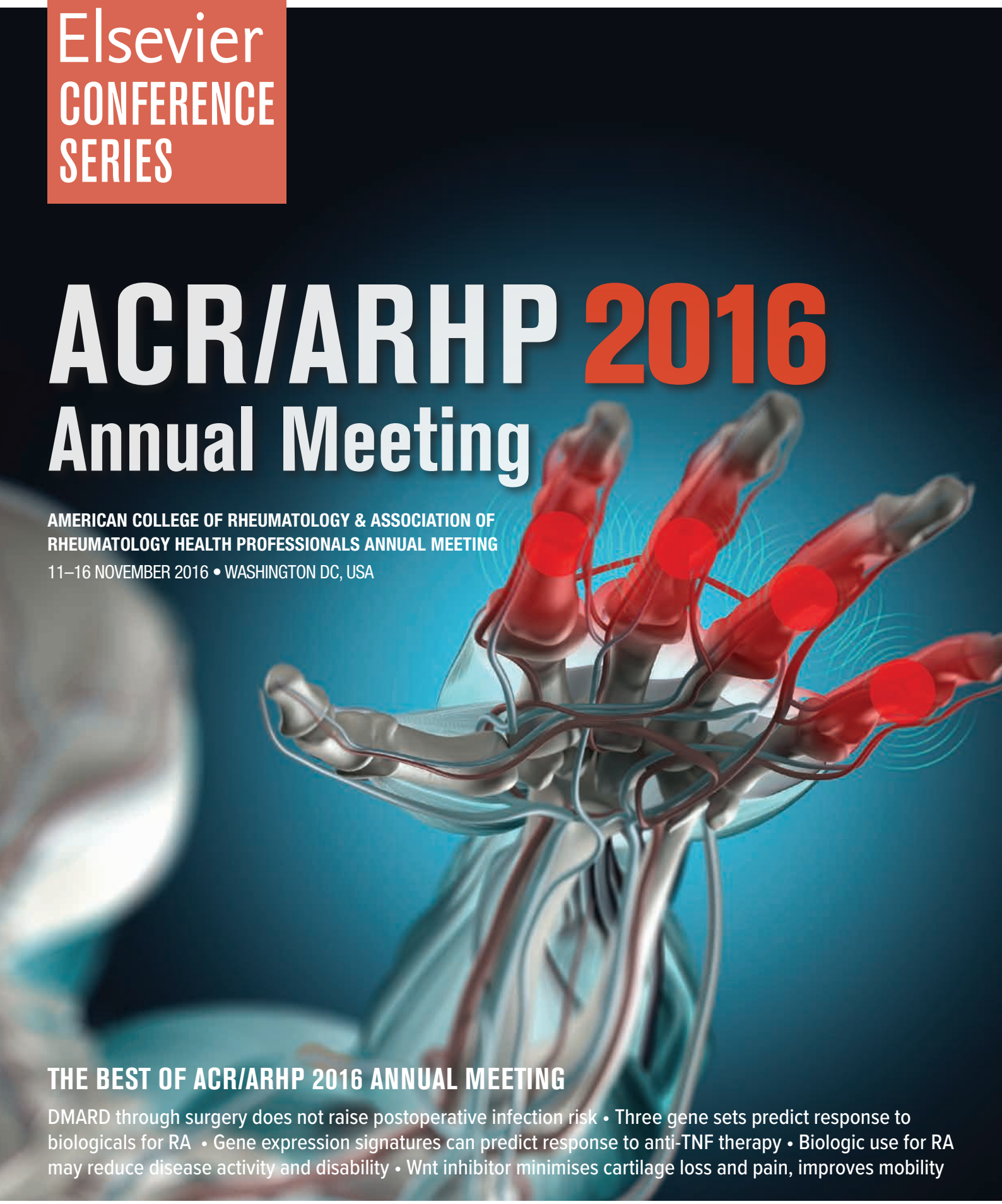
11–16 NOVEMBER 2016 • WASHINGTON DC, USA



THE BEST OF ACR/ARHP 2016 ANNUAL MEETING

DMARD through surgery does not raise postoperative infection risk • Three gene sets predict response to biologicals for RA • Gene expression signatures can predict response to anti-TNF therapy • Biologic use for RA may reduce disease activity and disability • Wnt inhibitor minimises cartilage loss and pain, improves mobility

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*Please note changes in Product Information.

References: 1. SIMPONI® Product Information (20 September 2016). **2.** Keystone EC *et al. J Rheumatol* 2016;43(2):298–306.

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Changing paradigms in rheumatology

Welcome to our special coverage of the American College of Rheumatology and Association of Rheumatology Health Professionals Annual Meeting, part of the Elsevier Conference Series, that aims to bring you key clinical and scientific news from the world's top medical congresses.

This special ACR/ARHP 2016 Annual Meeting, kindly brought to you through advertising by Janssen Australia, brings together leading research from the top guns who are changing paradigms in rheumatology. Our Elsevier Australia news team has independently reported from the 4000 poster and oral presentations on show to bring you the best ACR/ARHP 2016 Annual Meeting, has to offer.

Topics, we selected, that are creating this paradigm shift include:

- New thinking on biologics in RA
- Use of DMARDs through RA surgery
- Intensive management regimes to reduce RA disease activity
- Importance of early diagnosis and treatment for RA remission
- Increased CV risk for RA patients
- Emergence of gene expression signatures, and
- Promise of Wnt inhibitors in OA

We hope you enjoy this issue of the Elsevier Conference Series.

Anne Neilson
Managing Editor
Elsevier Conference Series

Biologic therapy continues in 12% RA patients despite cancer diagnosis

In a cohort of patients with rheumatoid arthritis who were diagnosed with cancer, 12% either continued their biologic or started a new biologic. The biologic most commonly in question was a tumour necrosis factor inhibitor. One third harboured active cancer or a recurrence during follow-up.

Natalia V. Zamora, MD, of the University of Texas MD Anderson Cancer Centre, Houston, explained that biologics for rheumatoid arthritis suppress immune response. Immune response is key for protection against cancer progression, and biologics are often discontinued when a patient with rheumatoid arthritis develops cancer for this reason.

Dr Zamora noted, "One of the major discussions in rheumatology is whether to continue or suspend a biologic in certain conditions, one of which is cancer." At Dr Zamora's centre, a large number of patients present with both conditions.

Dr Zamora and coinvestigators set out to assess the extent to which biologics are continued or begun a new therapy in patients with rheumatoid arthritis who are diagnosed with cancer.

Between 2002 and 2014, study participants with rheumatoid arthritis and cancer were seen at a National Cancer Institute Comprehensive Cancer Center. They were initially identified as suffering from rheumatoid arthritis if they had submitted an insurance claim with the diagnostic code for rheumatoid arthritis (714) according to the International Classification of Diseases 9.

Dr Zamora's team scanned electronic medical records for patients who fulfilled the following criteria in addition to their claim code:

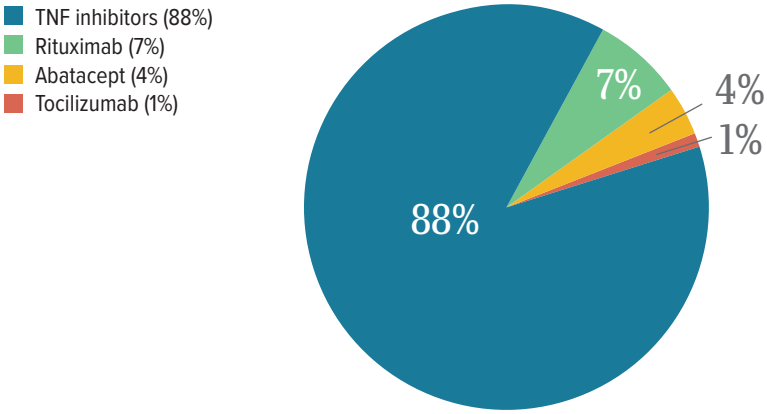
- Age ≥18 years
- A diagnosis of rheumatoid arthritis with or without current or past treatment with a disease-modifying antirheumatic drug or biologic. Patients with more than one primary or nonmelanoma skin cancer were excluded.

Descriptive statistics were used to summarise patient characteristics, biologic use, and time to the start of biologic treatment onset after they were diagnosed. Kaplan-Meier analysis was used to determine time from biologic therapy onset to cancer recurrence.

A total of 1719 patients were included, of whom 563 had received biologic therapy before and/or after their cancer diagnosis. Most participating patients were female (72%), and were a mean of 59 ± 13 years of age at cancer diagnosis.

Eighty-one patients underwent follow-up <3 months after their cancer diagnosis. These patients were not included in the study. Forty-three discontinued biologic therapy before being diagnosed with cancer; and 313 were receiving biologic therapy at the time they were diagnosed. Of this group, 225 (72%) stopped their biologic within 3 months of diagnosis, and 88 (28%) continued it.

Initiation biologics included:



In addition, 126 (58%) patients initiated a biologic after they were diagnosed with cancer, a median of 8 (range 0.04–39) years later. Overall, 214/1719 (12%) of the cohort took a biologic after their cancer diagnosis. Forty-two percent of those 214 patients were taking a biologic before they were diagnosed with cancer, and they continued it.

The most common primary cancer site among the 214 patients was the breast (28%), followed by lymphoma and the prostate in 7% each, and melanoma in 6%.

Almost 20% of patients switched biologic therapy at a later stage. Fifty-seven patients (27%) patients who took a biologic harboured active cancer or developed a recurrence during follow-up, and 14 (7%) died.

Twelve percent of the cohort suffered recurrent or active cancer the first year after beginning biologic therapy (or after cancer diagnosis, if the biologic had been maintained). Sixteen percent experienced recurrent or active cancer by 2 years, and 33% by 5 years.

Dr Zamora said that 12% of this cohort of patients with rheumatoid arthritis continued to take a biologic after they had been diagnosed with cancer. The biologic was most frequently a tumour necrosis factor inhibitor. One third harboured active cancer or a recurrence during follow-up.

Dr Zamora put forward the need for additional controlled studies to determine whether patients with rheumatoid arthritis who receive a biologic after developing cancer are at higher risk of cancer recurrence. "Patients who took a biologic after cancer diagnosis might be compared with a control group without rheumatoid arthritis, matched by cancer characteristics, sex, and age," she suggested.

> "One of the major discussions in rheumatology is whether to continue or suspend a biologic in certain conditions, one of which is cancer.

DMARD through surgery does not raise postoperative infection risk

Patients with rheumatoid arthritis who stay on their disease-modifying antirheumatic drug through surgery do not raise their risk of postoperative infection, concludes a retrospective database analysis.

Hsin-Husan Juo, MD, of the University of Washington School of Medicine, Seattle, explained that it is often recommended that patients with rheumatoid arthritis stop their disease-modifying antirheumatic drugs (DMARDs). The agents are immunosuppressive.

Dr Juo and colleagues assessed the risk of postoperative infections in patients with rheumatoid arthritis who continue DMARD therapy. They examined data from 9362 surgeries performed on 5544 patients with rheumatoid arthritis to assess this risk.

Dr Juo commented, "Patients experience a greater possibility of flare-up if they discontinue their medication for rheumatoid arthritis for a period prior to surgery. Those who experience flares are usually required to take prednisone to calm the inflammation. It then takes another 2 to 3 months for either DMARDs or tumour necrosis factor inhibitors to be become fully effective after restarting them."

"Prednisone is known to delay wound healing and raise infection rates, increasing postsurgical complications. Whether discontinuing DMARDs or tumour necrosis factor inhibitors before elective surgery is needed, therefore, is an important question."

Using US Department of Veterans Affairs databases and a surgical quality registry, Dr Juo and colleagues identified surgical procedures performed on patients with rheumatoid arthritis between 1999 and 2009. Patients had been taking at least one DMARD or biologic drug, for example, tumour necrosis factor (TNF) inhibitors, before surgery.

Using this information provided by Veterans Affairs pharmacy database records, a validated algorithm was used to determine whether patients stopped their medication before surgery or stayed on therapy. Patients were grouped according to therapy:

- Methotrexate alone
- Hydroxychloroquine alone
- Leflunomide alone
- Methotrexate + a tumour necrosis factor inhibitor.

The researchers then tallied total infectious complications and wound infections of the above groups.

Patients with rheumatoid arthritis remained on DMARD therapy despite their risk of infection. The therapy was continued in 1961 of 2600 surgeries performed in patients taking methotrexate alone; in 1496 of 2012 surgeries performed in patients taking hydroxychloroquine alone; and in 508 of 652 surgeries performed in patients taking leflunomide alone.

In patients who were taking both methotrexate and a TNF inhibitor, they stayed on both drugs in 196 of 386 surgeries. In 59 surgeries, patients stopped methotrexate and stayed on their TNF inhibitor.

TNF inhibition was stopped and methotrexate continued in 72 surgeries. In 59 surgeries, both agents were stopped. Continuing a DMARD before surgery was not associated with increased rates of overall postoperative infections or wound infections in any of the various treatment groups.

Dr Juo said, "Discontinuing methotrexate, hydroxychloroquine, leflunomide monotherapy, and a TNF inhibitor plus methotrexate therapy was not associated with increased risk of postoperative infection."

She added, "Surgeons and rheumatologists should consider recommending that their patients with rheumatoid arthritis continue medication perioperatively to better control rheumatoid arthritis. Persistence of therapy will decrease the possibility that a steroid will be needed and maintain better postoperative functioning."

Dr Juo and colleagues plan to extend the study and analyse more specific surgery subgroups, as well as more biological therapies, with a view toward gaining more insight into infection risk with maintenance of disease-modifying therapies for patients with rheumatoid arthritis.

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Intensive treatment for RA reduces disease activity

Intensive management regimens for rheumatoid arthritis have been shown to be associated with progressive improvement in disease activity, function, and quality of life. Improvements are seen across all strata of disease activity levels with less active disease and more remissions.

Nicola J Gullick, MD, of King's College London, UK, explained that intensive treatment of rheumatoid arthritis has been increasingly emphasised with little direct evidence of the impact of such strategies on long-term outcome. Dr Gullick and colleagues set out to evaluate disease activity and outcomes of a regimen aiming to treat to a target Disease Activity Score 28 <2.6.

This single-centre, prospective, observational cohort study covering a 10-year period, involved 1693 patients seen on 10,773 occasions between 2005 and 2015. At the first visit, mean patient age was 55 years and mean disease duration 10 years. Disease-modifying antirheumatic drugs often in combination, and a range of biologics were prescribed. Disease Activity Score 28, Health Assessment Questionnaire, and quality of life according to the EuroQol 5D were recorded at each visit. Temporal changes were assessed by descriptive statistics and maximum-likelihood regression models.

To further understand outcomes in different mean Disease Activity Score 28 categories, the investigators also assessed a subgroup of 714 patients with three to five follow-up visits between 2010 and 2015 (6728 visits). Mean scores on the Health Assessment Questionnaire and EuroQol 5D were assessed for each treatment group.

Mean 10-year follow-up Disease Activity Score 28 scores fell from 4.1 to 3.7 between 2005 and 2015. Mean Health Assessment Questionnaire score fell from 1.26 to 1.15 and mean EuroQol 5D scores improved from 0.47 to 0.56. Regression models showed annual changes for Disease Activity Score 28 scores were –0.03 (95% CI –0.04–0.02); Health Assessment Questionnaire score –0.019 (95% CI –0.025–0.013); and EuroQol 5D 0.006 (95% CI 0.003–0.008).

The number of patients with high disease activity (Disease Activity Score 28 >5.1) decreased from 25% to 16% while Disease Activity Score 28 remission increased from 18% to 27%. The four components of Disease Activity Score 28 showed divergent patterns of change. Mean swollen joint count fell from 3.1 to 2.1 (33%), mean erythrocyte sedimentation rate fell from 25 to 18 (26%), and mean tender joint count fell from 5.0 to 4.5 (12%).

Mean patient global responses increased by 9% (43.2 to 47.1). Impact-of-Disease Activity Score 28 category 154/714 (22%) demonstrated persistent high disease activity. Compared with patients in remission, Health Assessment Questionnaire score was increased by 1.06, and EuroQol 5D reduced by 0.27.

All groups used disease-modifying antirheumatic drugs at a similar rate, including combination disease-modifying antirheumatic drugs. Only 64 (9%) patients with persistent high disease activity were receiving biologics, versus 18–20% of other groups (P = 0.034). This variation resulted from failure to respond to biologics, unwillingness to take them, or contraindications to their use.

Dr Gullick concluded that intensive management regimens for rheumatoid arthritis were shown to be associated with progressive improvement in disease activity, function, and quality of life. Improvements are seen across all strata of disease activity levels with less active disease and more remissions. Patient global scores do not improve, however, requiring further investigation.

A minority of patients suffer continued high disease activity with substantial disability and reduced quality of life. This group of patients are less likely to receive biologics. Individualised strategies may be required for this group, including novel therapies or psychological interventions.

Glucocorticoids increase fracture-risk in RA patients

Two analyses of the TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOWer morbidity and mortality (TOMORROW) study have shown that glucocorticoid use is a predictor of fractures in patients with rheumatoid arthritis. Patients should be tapered off these agents once their disease activity has been controlled.

Kenji Mamoto, MD, of the Osaka City University Graduate School of Medicine, Osaka, Japan, explained that patients with rheumatoid arthritis who suffer from muscle weakness and stiff or painful joints might be at increased risk of falls and fractures.

He and colleagues set out to prospectively determine the incidence of clinical fractures and associated predictors in patients with rheumatoid arthritis who participated in the TOMORROW study, which began in 2010.

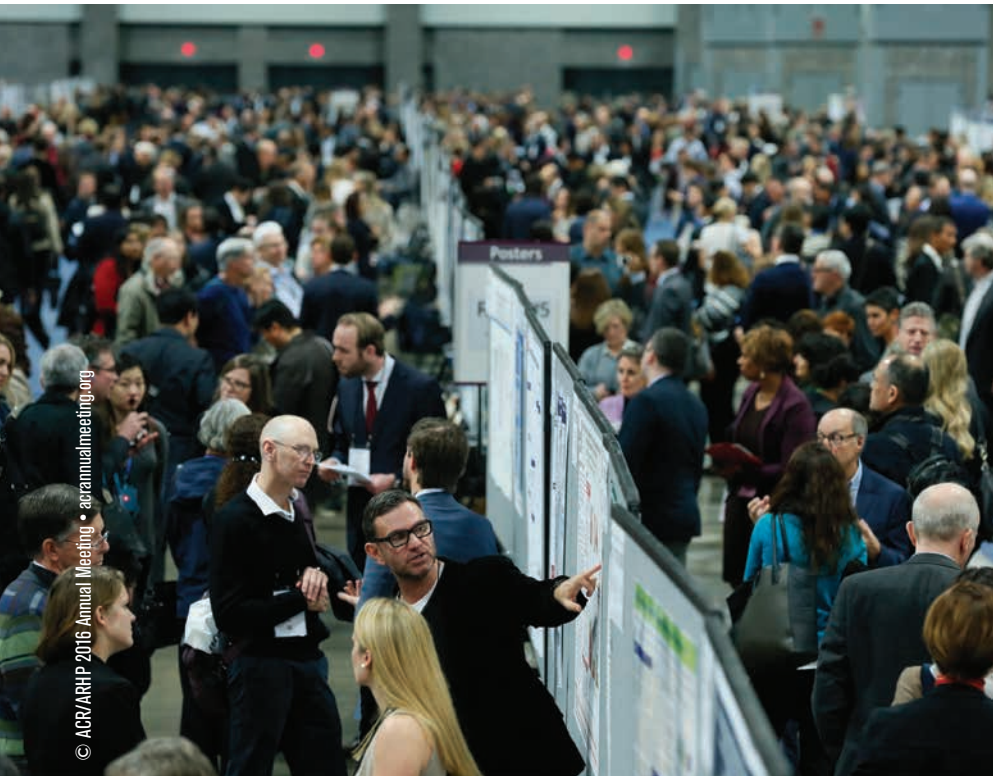
The investigators evaluated anthropometric parameters, bone mineral density, disease activity, medication for rheumatoid arthritis, and the incidence of clinical fractures over a 5-year period in 202 patients (mean age, 58.6 years; medication with biological agents, 54.9%) and 202 age- and sex-matched healthy volunteers (controls; mean age, 57.4 years).

They compared the incidence of clinical fractures between patients and controls between 2010 and 2015 and analysed associated predictors using Cox proportional hazard regression analysis.

The incidence of clinical fractures did not significantly differ between patients with rheumatoid arthritis (0.042 per person-year) and controls (0.034 per person-year) within the 5-year period. Also, fracture sites did not differ between the two groups.

Multivariable Cox proportional hazard regression analysis adjusted for confounding factors including age, sex, smoking, and body mass index revealed that low bone mineral density of the thoracic vertebrae (<0.7 g/cm^2) at entry was significantly associated with the incidence of clinical fractures (hazard ratio 2.63; 95% CI 1.49–4.66; P = 0.001) in all participants.

Though medication with a glucocorticoid at entry was also a significant risk factor for fractures (hazard ratio 2.14; 95% CI 1.24–3.68; P = 0.006), Morbidity due to rheumatoid arthritis was not (hazard ratio 1.22; 95% CI 0.74–2.01).



Among patients with rheumatoid arthritis, low bone mineral density of the thoracic vertebrae (<0.7 g/cm^2) at entry was the most prominent risk factor for fractures (hazard ratio 3.53; 95% CI 1.52–8.15; P = 0.003).

Additionally, medication with a glucocorticoid at entry (hazard ratio 2.46; 95% CI 1.28–4.73; P = 0.007) was a significant risk factor for fractures. A mean glucocorticoid dosage of ≥ 2 mg daily during the 5-year period increased risk for fractures in the patients (hazard ratio 2.67; 95% CI 1.06–6.72; P = 0.037).

Dr Mamoto and colleagues then set out to assess the effects of decreasing the dosage of glucocorticoids and the incidence of clinical fractures in patients with rheumatoid arthritis based on 5-year findings of the TOMRROW study.

Clinical fractures in patients with rheumatoid arthritis was 0.042 per person-year. Eighty-four patients with rheumatoid arthritis (41.6%) treated with a glucocorticoid experienced

a significantly higher incidence and number of clinical fractures than those who did not take a glucocorticoid (27.4% vs 11.9%; P = 0.008; 0.063 vs 0.012 per person-year; P = 0.012, respectively).

After adjusting for confounding factors including age, sex, smoking, and body mass index, multivariable Cox proportional hazard regression analysis revealed that glucocorticoids administered within the 5-year period were a significant risk factor for clinical fractures (hazard ratio 2.35; 95% CI 1.18–4.68; P = 0.015).

An average glucocorticoid dose during the 5-year period of ≥2 mg daily increased risk for fractures in patients with rheumatoid arthritis (hazard ratio 2.67; 95% CI 1.06–6.72; P = 0.037).

Though reducing the glucocorticoid dose alone did not decrease the risk of clinical fractures in patients with rheumatoid arthritis (hazard ratio 0.75; 95% CI 0.31–1.82), risk was significantly decreased when the glucocorticoid dose was reduced to zero within the 5-year period (hazard ratio 0.28; 95% CI 0.11–0.72; P = 0.008).

Dr Mamoto concluded that no difference was observed in the incidence of clinical fractures between patients with rheumatoid arthritis and controls over a 5-year period. Low bone mineral density of the thoracic vertebrae and low glucocorticoid doses (≥2 mg daily) are apparently significantly associated with the incidence of clinical fractures among patients with rheumatoid arthritis.

He added that medication with glucocorticoids was a significant risk factor for clinical fractures. Achieving freedom from glucocorticoids among patients with rheumatoid arthritis within 5-years could decrease their risk of clinical fractures. Glucocorticoid medication should be tapered to zero over a period of 5 years in patients after disease activity becomes well controlled.

More patients with RA achieve radiographic remission 10 years post diagnosis

The proportion of patients who achieve radiographic remission 10 years after their diagnosis of early rheumatoid arthritis has been on the rise over recent years results of a prospective, single-centre study reveal.

Tuulikki Sokka, MD, PhD, of Jyväskylä Central Hospital, Jyväskylä, Finland, explained that in rheumatoid arthritis, x-rays of the hands and feet are an objective outcome measure. Cumulative disease activity over years results in joint damage.

Unlike other clinical measures of rheumatoid arthritis, radiographic damage is caused mainly by inflammation. X-rays are an efficient way to measure long-term outcomes of patients with the disease.

Dr Sokka and coinvestigators analysed radiographic remission in patients with early rheumatoid arthritis 10 years after diagnosis.

A total of 1046 patients were diagnosed with rheumatoid arthritis from 1997 to 2005. They were scheduled for 10-year follow-up including hand and foot x-rays. They had also been x-rayed at years 0, 2, 5. Larsen scoring from 0–100 was performed of the metacarpophalangeal joints, wrists, and two to five metatarsophalangeal joints.

Radiographic remission was defined as no new erosions and no worsening erosions from baseline (at diagnosis) through 10 years. Patients with a new diagnosis of rheumatoid arthritis in 1997–1999, 2000–2002, and 2003–2005 were compared regarding the proportion with radiographic remission or no remission 10 years after diagnosis.

Among 1046 patients (66% women, mean age 58 years, 60% seropositive, 13% with erosions at baseline), 743 (70% women, mean age 54 years, 65% seropositive, 12% with erosions at baseline) attended their 10-year follow-up visit. Among 480 seropositive patients, median progression of Larsen score was 3 (interquartile range 0, 8). In 263 seronegative patients, median progression of Larsen score was 0 (interquartile range 0, 2).

At the follow-up visit after 10 years, radiographic remission had been achieved in 31%, 40%, and 56% of seropositive patients diagnosed in 1997–1999, 2000–2002, and 2003–2005, respectively; P < 0.001. In seronegative patients, these percentages of patients who had achieved radiographic remission were 75%, 79%, and 83%, respectively.

Over the 10-year period, methotrexate was taken by 79%, 84%, and 90% of patients diagnosed in 1997–1999, 2000–2002, and 2003–2005, respectively. Subcutaneous methotrexate was taken by 13%, 24%, and 25%; sulfasalazine by 82%, 83%, and 72%; hydroxychloroquine by 61%, 73%, and 76%; leflunamide by 13%, 16%, and 14%; intramuscular gold by 19%, 11% and 5%; prednisone by 63%, 80%, and 82%; and biologic agents in 10%, 16%, and 19% of patients, respectively.

Fifteen percent of women and 30% of men died over the 10-year period, and death was the main cause of missing data.

Dr Sokka concluded that the proportion of patients with early rheumatoid arthritis who achieve radiographic remission 10 years after diagnosis of early rheumatoid arthritis has been rising over recent years. A majority with seropositive rheumatoid arthritis seen at 10-year follow-up in 2013–2015 achieved radiographic remission.

Over the 10-year period, methotrexate, subcutaneous methotrexate, hydroxychloroquine, prednisone, and biologics were taken at higher rates. Sulfasalazine and intramuscular gold were prescribed at a declining rate.

New findings suggest mortality risk may be reduced in RA patients with lung disease

First-line rituximab treatment may lead to longer survival in patients with rheumatoid arthritis and lung involvement versus a tumour necrosis factor inhibitor, results of a prospective comparison study show.

Kimme Hyrich, MD, PhD, of the University of Manchester, UK, explained that mortality rates are higher in patients with rheumatoid arthritis with lung involvement. It is not common for patients with rheumatoid arthritis to experience pulmonary complications such as interstitial lung disease, but the combination raises mortality rates.

Tumour necrosis factor (TFN) inhibition has been suggested to be linked to the development of or worsening of interstitial lung disease in patients with rheumatoid arthritis.

The British Society for Rheumatology advised against TNF inhibition in patients with rheumatoid arthritis and interstitial lung disease in 2005. Yet, at that time, no data was available on whether rituximab would reduce mortality or lead to the development or exacerbation of interstitial lung disease.

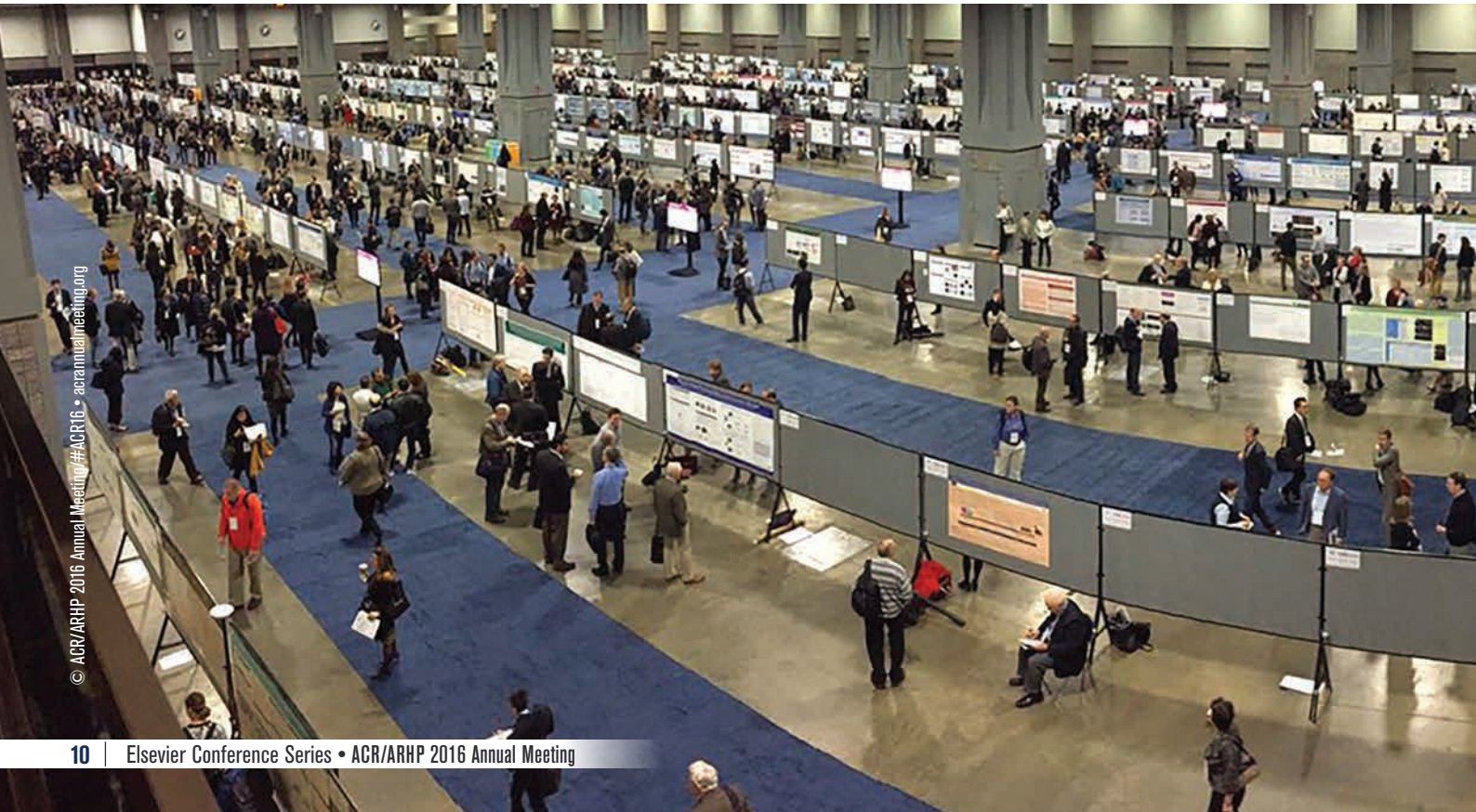
Dr Hyrich and colleagues set out to assess and compare mortality rates among patients with rheumatoid arthritis and interstitial lung disease who had begun therapy with either rituximab or a TFN inhibitor as their first biologic. The team also examined causes of death.

They employed data on participants in the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis.

Dr Hyrich noted, "Treatment of underlying arthritis among patients with rheumatoid arthritis and interstitial lung disease can be complicated, because methotrexate is often contraindicated. The best choice of biologic therapy for patients with rheumatoid arthritis and interstitial lung disease and active arthritis is unclear given the relative contraindication for TFN inhibition."

The team calculated death rates per 1000 person-years. Censoring occurred at death, as of December 2015, or 5 years after the patient's first registration, whichever of these factors came first. They also examined the frequency of interstitial lung disease mentions on death certificates.

They then generated Kaplan-Meier survival curves with risk comparisons between rituximab and TFN inhibitor cohorts using Cox regression and an exposure model, adjusted for potential confounders. They



evaluated the eligibility of confounders by clinically relevant justification or statistical significance, after adjusting for treatment effects.

The study cohort was composed of 353 patients with rheumatoid arthritis and interstitial lung disease. A total of 310 were treated with TFN inhibition and 43 with rituximab. All had been recruited prior to 2008. During the first 5 years of follow-up, 76 patients died in 804.9 person-years in the cohort whose therapy began with TFN inhibition, and eight died in 156.7 person-years among those who began with rituximab.

Death rates were 94.4 (74.4–118.1) and 51.0 (22.0–100.5) per 1000 person-years, respectively. Interstitial lung disease had been noted in 36.5% of 74 death certificates of patients in the TFN inhibitor cohort and in all of the three death certificates of those in the rituximab cohort.

Dr Hyrich asserted that the unadjusted mortality risk in patients treated with rituximab was numerically half of that in patients treated with a TFN inhibitor, though the difference was not statistically significant. Adjustment for baseline age, sex, disability, disease activity, and disease duration had little effect on these estimates.

> "We will need to collect more data from patients with this history, to further understand this issue. Rheumatoid arthritis with interstitial lung disease is rare. Without robust studies, the decision of the best choice of therapy to treat the underlying arthritis will need to be based on anecdotal evidence.

Patients with rheumatoid arthritis and interstitial lung disease who began therapy with rituximab appeared to be at lower mortality risk than those who began therapy with a TFN inhibitor first, though the two groups did not differ statistically significantly.

The registry did not contain enough information on disease severity or subtype of interstitial lung disease, so drawing conclusions on the relative safety of these two therapies was difficult. Clarifying safety issues of these therapies in patients with rheumatoid arthritis and interstitial lung disease will need larger, more detailed studies.

Dr Hyrich concluded, "The upshot is that death rates among patients with rheumatoid arthritis and interstitial lung disease who began with rituximab as their first biologic were lower than in those who began therapy with a TFN inhibitor. We adjusted for age, gender, disease duration, and Health Assessment Questionnaire results, and the two cohorts still differed. These factors are important determinants of mortality."

"Since we did not have data on lung disease severity, however," she said, "which is an important risk factor for mortality, it was difficult to determine whether rituximab was a better treatment option in patients with rheumatoid arthritis and interstitial lung disease, without clinical trial data."

She added, "We will need to collect more data from patients with this history, either separate from or within national registries, to further understand this issue. Rheumatoid arthritis with interstitial lung disease is rare. Without robust studies, the decision of the best choice of therapy to treat the underlying arthritis will need to be based on anecdotal evidence."

Three gene sets predict response to biologicals for RA

Three gene expression signatures may help identify response to tumour necrosis factor inhibitors and B-cell depletion therapies in patients with moderate to severe rheumatoid arthritis.

This conclusion is based on results of serological RNA sequencing of patients in the Optimal management of Rheumatoid arthritis requiring Biologic Therapy (ORBIT) study.

ORBIT was a randomised, controlled trial of patients with rheumatoid arthritis in the UK. Duncan Porter, MD, of Queen Elizabeth University Hospital, Glasgow, UK, drew on data from ORBIT to seek gene expression signatures that would help predict response to either tumour necrosis factor (TNF) inhibitors or rituximab, or both.

> "If we could identify blood markers that could predict which agent patients are most likely to respond to, we could choose the optimal therapy to start that patient on, instead of relying on trial and error.

Dr Porter commented, "The ORBIT data showed that the likelihood of patients with seropositive rheumatoid arthritis to respond to rituximab is comparable to their likelihood of responding to tumour necrosis factor inhibition. A significant proportion of patients failed to respond to their first biologic drug but responded when switched to the alternative."

"If we could identify blood markers," he said, "that could predict which agent patients are most likely to respond to, we could choose the optimal therapy to start that patient on, instead of relying on trial and error."

Dr Porter and coinvestigators sequenced the RNA from the peripheral blood of 241 rheumatoid arthritis patients who participated in ORBIT. They first depleted ribosomal and globin RNA then used 70% of samples to develop prediction models of response. They reserved 30% of samples to validate their findings.

Clinical response was defined as a reduction in Disease Activity Score 28–erythrocyte sedimentation rate of 1.2 units from baseline to 3 months. Multiple machine learning tools were used to predict general responsiveness and differential responses to TNF inhibition and to rituximab.

They employed tenfold cross-validation to train the models for responsiveness, then tested these on the validation samples.

Support vector machine recursive feature elimination was used to identify three gene expression signatures predictive of response. Eight genes predicted general responsiveness to both TNF inhibition and rituximab, 23 genes predicted responsiveness to TNF inhibition, and 23 genes predicted responsiveness to rituximab.

Their prediction models were then tested on the validation set. This test yielded receiver operating characteristic plot points with an area under the curve of 91.6% for general responsiveness, 89.7% for response to TNF inhibition, and 85.7% for response to rituximab.

Dr Porter said, "These gene expression markers indeed predicted drug-specific response. If confirmed, it will be possible to stratify patients into groups more likely to respond to one drug than to the other. This stratification will confer higher response rates and a less likelihood of being prescribed an ineffective drug. Ineffective treatment is associated with pain, stiffness, disability, and diminished quality of life, so this identification of the optimal therapy will lead to improved care".

He stated that confirmation of these models will be the next step.

"We hope to confirm the findings with targeted RNA sequencing, via internal validation. Then we will test a new cohort of patients (external validation). The ultimate goal is to develop a commercial testing kit that will allow clinicians to be guided toward the most effective treatment before their patients begin therapy."

Gene expression signatures can predict response to anti-TNF therapy

Monocyte gene expression signatures in patients with rheumatoid arthritis can help predict whether these patients will respond to tumour necrosis factor inhibitors. Such signatures may enable a more personalised approach to therapy for patients with rheumatoid arthritis. This conclusion is based on results of an analysis of single cell gene expression.

Theresa L. Wampler Muskardin, MD, of the Mayo Clinic, Rochester, Minnesota, explained that diagnosing and initiating effective therapy early is important in rheumatoid arthritis.

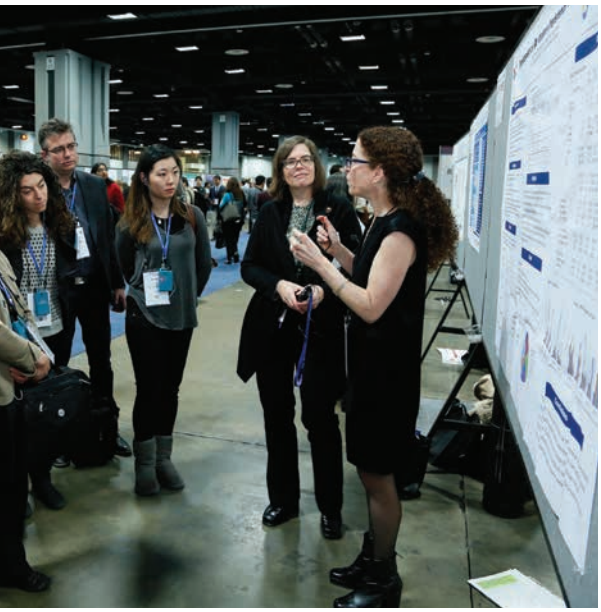
Dr Wampler Muskardin and coinvestigators expanded on their recent findings showing that pretreatment serum type 1 interferon β/α ratio >1.3 could predict response to tumour necrosis factor (TNF)-alpha inhibition. They conducted this new study to evaluate the cellular mechanisms of this response.

Dr Wampler Muskardin asserted, "We wanted to better understand the impact of the type I interferon ratio that predicts nonresponse to TNF inhibition on a major inflammatory cell type in rheumatoid arthritis. When we analyse whole blood or mixed cell populations, we may miss the effects of type I interferon on single cells and immune cell subtypes".

She continued, "Using single-cell gene expression technology, we hoped to find differences between responders and nonresponders in their expression of select genes. These differences may potentially lead to a blood test to facilitate treatment decisions in patients with rheumatoid arthritis before they start biologic therapy."

The researchers investigated whether monocyte gene expression differed significantly among patients with rheumatoid arthritis based on their pretreatment blood serum type 1 interferon β/α ratio. They isolated single classic and single nonclassic blood-derived monocytes from 15 seropositive patients with rheumatoid arthritis before TNF inhibition was initiated.

Patients were divided into two groups according to pre-TNF inhibitor serum ratio: six patients with interferon β/α >1.3 and nine with interferon β/α <1.3. They performed unsupervised hierarchical clustering of 87 target genes on the single monocytes.



JAK1 and interleukin 1A were found to differentiate strongly between the two groups. In nonclassic cells only, STAT2, interleukin T7, PKR, TLR7, and IRAK1 expression was more likely in nonresponders. In classic cells only, IFIT2 and CD36 expression was more likely. According to multivariate logistic regression analysis, interleukin 1A, CD32a, interleukin 8, TYK2, and IRAK1 nonclassic plus classic monocytes aligned with treatment response.

Compared with the mixed monocyte model, interleukin 8 and IRAK1 in nonclassic, and CXCR3 in classic monocytes exhibited even stronger alignment with treatment response. STAT2 predicted response strongly in nonclassic cells alone. CXCL9 predicted response strongly in classic cells alone.

Previous work done by Dr Wampler Muskardin's team showed that a ratio of interferon β/α >1.3 is predictive of nonresponse to TNF inhibition in patients with rheumatoid arthritis. In the present study, gene expression in monocyte subsets was shown to differ in patients with rheumatoid arthritis with an interferon β/α ratio >1.3, the ratio of type I interferons that predicts nonresponse to TNF inhibition.

Dr Wampler Muskardin concluded, "The difference between therapy response groups was strongest when subsets of monocytes were analysed separately rather than together, and distinct expression signatures were identified in those subsets."

She continued, "The difference in strength between therapy response groups suggests that investigating these biological pathways in monocyte subsets will bring further insight into the biological process that determines response to TNF inhibition in rheumatoid arthritis. Such an investigation may identify additional therapeutic targets or other more easily measurable markers that can predict response to TNF inhibition."

Dr Wampler Muskardin asserted that future studies should focus on monocyte subsets that may identify molecular differences determinative of treatment response to TNF inhibition. In the future, clinicians may be able to tailor therapy to patients with rheumatoid arthritis based on the underlying biology of their disease.

Earlier diagnosis, treatment of RA needs improvement to achieve remission

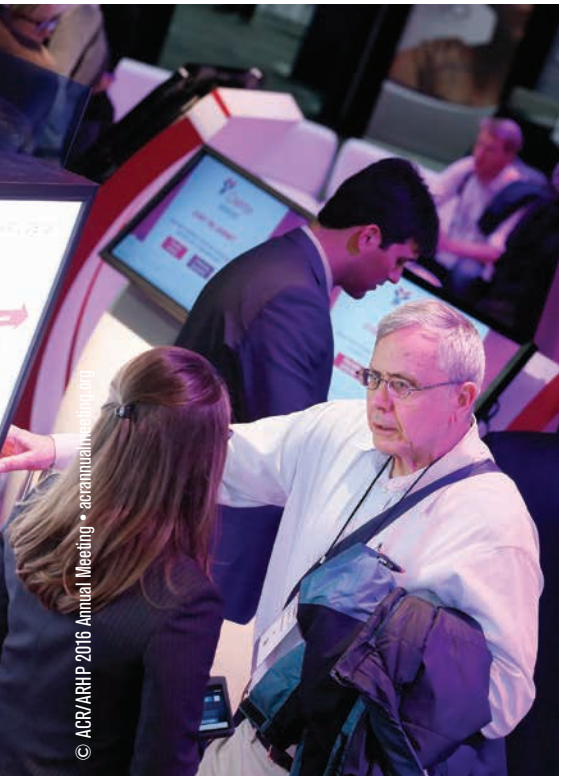
Two retrospective reviews have demonstrated that, while rheumatoid arthritis remission rates have improved over the past few decades, a shorter time to diagnosis and initiation of early effective treatment need to be improved.

Justine Vix, MD, of University Hospital Poitiers, Poitiers, France, examined stable remission of rheumatoid arthritis over a 7-year period and factors predictive of a positive outcome in two retrospective chart reviews.

She explained that remission is the best achievable state in rheumatoid arthritis. When remission is a goal, it needs to be maintained.

"I would like to see improved treatment," Dr Vix remarked, "and optimisation of quality of life. I hope to avoid pain, joint damage, bone erosion, deformation, and impaired functioning."

Dr Vix and colleagues analysed clinical, biological, immunogenetic, and radiographic records of 364 patients with active rheumatoid arthritis. All were seen in 2008 and met American College of Rheumatology criteria. Patients were a mean 62.9 years of age.



> "Remission is the best achievable state in rheumatoid arthritis. When remission is a goal, it needs to be maintained.

Patients were seen at least once a year during hospitalisation or in an outpatient clinic. The team collected data through 2015. Data were available for 232 patients (75%) who were followed for 7 years.

After 1 year, 97 patients (31%) achieved remission as defined by the American College of Rheumatology/European League Against Rheumatism, as Disease Activity Score 28 <2.6.

A total of 133 patients (57%) achieved remission after 1 year. Their mean activity per Disease Activity Score 28 was 3.44 and decreased to 2.67 after 7 years of follow-up. Thirty-eight percent of the cohort stopped taking corticosteroids.

The remission rate (Disease Activity Score 28 <2.6) of 31% after 1 year remained stable in 76% of patients. Including those not in remission after 1 year, 48.6% achieved remission during follow-up and 17% remained in low disease activity (Disease Activity Score 28 <3.2) in 2015.

Conventional, given alongside biological disease-modifying antirheumatic drugs, especially tumour necrosis factor inhibitors, were associated with more frequent long-term remission.

Dr Vix concluded that 76% of patients who achieved remission after 1 year maintained their long-term remission. Targeted, combination conventional and biologic disease-modifying antirheumatic drugs induced a higher rate of long-term remission.

Jon Thorkell Einarsson, MD, of Lund University, Lund, Sweden, examined the impact of changing therapeutic goals in national guidelines on sustained remission, according to Disease Activity Score 28 <2.6 on at least two consecutive 6-month periods.

He explained that remission has become a therapeutic goal in rheumatoid arthritis, especially since biologics were introduced in 1999. The Swedish Quality Registry is a national registry for rheumatic diseases in which all 64 rheumatology units in the country participate.

All adult patients with rheumatoid arthritis included in the registry from 1992–2013, who were followed through 2014 with at least three visits, were eligible (n=29,084). Median patient age was 59.6 years and 72% of patients were women. Symptoms began from 1934 through 2012. In parts of the comparisons, only patients whose symptoms began between 1999 and 2009 were studied.

Median time from symptom onset to inclusion in the study was 2.6 (range 0–78) years. The last follow-up visit was a median of 10.5 years after symptoms had begun. Ninety-five percent of patients fulfilled American College of Rheumatology 1987 classification criteria for rheumatoid arthritis and 73.2% tested positive for anti-citrullinated protein antibodies.

Visits took place at median intervals of 6 (range 1 to 215) months. The duration of remission was defined as the time between the first visit that fulfilled remission criteria and the subsequent first

visit with higher disease activity, after a median of 2.8 years. Estimated time to sustained remission for each year was calculated using life table analysis and compared using the log-rank test.

At some point during follow-up, 12,193 (41.9%) patients reached sustained remission according to Disease Activity Score 28 at some time point during follow-up. Of those with symptom onset between 1981–1990, 1991–2000, and 2001–2010, 35.0%, 43.0% and 45.6% achieved sustained remission, respectively ($P < 0.001$ for each increment).

Time from symptom onset to sustained remission decreased every other year with only two exceptions ($P < 0.001$). Estimated mean time to sustained remission was 11.7 years in 1999 and 4.2 years in 2009.

Dr Thorkell Einarsson concluded that the prevalence of sustained remission was higher from 2001–2010 than during the two prior decades. Time from onset of symptoms of rheumatoid arthritis to sustained remission decreased gradually between 1999 and 2009.

The treatment strategy of the past decade improved outcomes, though improvement in time to diagnosis and early effective treatment is required to reach the goal of sustained remission in the majority of patients.

Cardiovascular risk comparable for patients with RA and those with T2D

Rheumatoid arthritis is linked to serious risk of cardiovascular events. Over a 15-year period, patients with rheumatoid arthritis have been shown to be at twice the risk of these events as those in the general population. These rates are similar to those associated with type 2 diabetes, concludes a retrospective database analysis.

Michael T. Nurmohamed, MD, PhD, of Vrije Universiteit Amsterdam, The Netherlands, wished to learn about the causes underlying increased mortality in patients with rheumatoid arthritis, as well as the severity of this risk.

He noted, "In daily clinical practice, it seemed that patients with rheumatoid arthritis suffered from myocardial infarctions more frequently than the general population. We began this study more than 15 years ago, when few data were available on cardiovascular morbidity in rheumatoid arthritis."

The investigators used data from the CARdiovascular research and RhEumatoid arthritis (CARRE) Study, a prospective cohort study investigating cardiovascular risk factors in a random sample of 353 patients with longstanding rheumatoid arthritis.

They assessed events related to heart disease after 3, 10, and 15 years of follow-up. Findings from these patients with rheumatoid arthritis were compared with data on glucose metabolism and cardiovascular risk factors from the Hoom study of 2540 individuals in the general population.

Risk of cardiovascular events in patients with established rheumatoid arthritis was more than twice that of the general population. Ninety-six patients with rheumatoid arthritis experienced a cardiovascular event during 2703 person-years of follow-up, an incidence rate of 3.6 per 100 person-years.

In the general population cohort, 298 persons suffered a cardiovascular event during a follow-up of 25,335 person-years, an incidence rate of 1.4 per 100 person-years. Of those 298 patients, 41 had diabetes mellitus. Age- and sex-adjusted hazard rates for cardiovascular events were higher for both rheumatoid arthritis and diabetes than for the cohort from the general population.

Elevated risk of myocardial infarction or stroke in people with established rheumatoid arthritis was found to be comparable to patients with type 2 diabetes. The increased cardiovascular risk in patients with rheumatoid arthritis remained elevated by as much as 70% compared to the cohort from the general population, even after adjusting for traditional heart disease risk factors. Chronic, systemic inflammation in rheumatoid arthritis was found to contribute independently to cardiovascular risk.

Dr Nurmohamed asserted, "Cardiovascular risk management is needed in rheumatoid arthritis, as in diabetes. Patients and their clinicians need to be aware of this risk and manage it. Patients with rheumatoid arthritis should target disease activity as well as traditional cardiovascular risk factors. Unfortunately, preventive measures against cardiovascular disease are poorly implemented in this population."

He remarked that effective treatment of systemic inflammation may address the increased risk of cardiovascular events and their attendant higher risk of mortality.

Dr Nurmohamed concluded that, "Evidence is accumulating that biologics reduce cardiovascular risk in rheumatoid arthritis. Tapering biologics, however, may expose patients to greater cardiovascular risk. We plan to conduct mechanistic studies on this possibility."

Improving cardiovascular risk prediction models by adding relevant biomarkers may also help practitioners better identify patients with rheumatoid arthritis who are most at risk of cardiovascular events and why. Such identification may lead to effective interventions.

Increased BMI with glucocorticoid treatment for early RA

After 12 weeks, patients with early rheumatoid arthritis who take methotrexate and glucocorticoids experience an increase in their body mass index more often than those who take methotrexate only, results of a prospective, comparative study show.

> "We hope to perform larger studies including more patients and to scan patients with dual-energy x-ray absorptiometry. This will enable us to measure not only total weight, but also specific indices, such as fat mass and fat-free mass and fat distribution.

Samina A. Turk, MD, of the Amsterdam Rheumatology and Immunology Center, The Netherlands, explained that glucocorticoids are a common initial treatment, in addition to methotrexate, just after a diagnosis of rheumatoid arthritis. Many patients, however, fear the weight gain associated with glucocorticoids.

Dr Turk and colleagues sought to assess the effect of glucocorticoids on body mass index (BMI) 4 and 12 weeks after initiation of therapy.

"I treat many patients with early rheumatoid arthritis," she said, "and after diagnosing their disease, I explain the medication we would like to prescribe. I prescribe methotrexate to all, but it takes time to affect disease activity. I recommend that patients with high disease activity or unfavourable prognostic factors take glucocorticoids for their rapid effect."

She added, "Despite their fast effect, many patients opt not to take glucocorticoids, because they fear weight gain. But I have observed that many patients who do not take glucocorticoids gain weight. I set out on this research to ascertain whether weight gain in these patients is caused by the disease or by the glucocorticoids."

Dr Turk and colleagues investigated consecutive patients in their cohort of patients with early arthritis. Disease duration was <2 years, at least two joints were swollen, and they had not received disease-modifying antirheumatic therapy.

Patients were divided into two groups:

- Patients were prescribed a glucocorticoid if they exhibited high disease activity and/or unfavourable prognostic factors. Those who took glucocorticoids were treated with methotrexate and the glucocorticoid (week 1: 30 mg; week 2: 20 mg; week 3: 15 mg; weeks 4–8: 10 mg; weeks 9–12: 7.5 mg)
- Those who did not take a glucocorticoid received methotrexate alone.

The 22 patients who did not take a glucocorticoid were matched in age to 22 patients who did take the drug. At baseline and weeks 4 and 12, weight, height, BMI, and Disease Activity Score 44 were recorded. Those with higher BMI were compared with those with a stable or lower BMI for statistical analysis.

Of the 44 patients with early rheumatoid arthritis, 24 were men. Mean patient age was 54 years. At baseline, patients who took versus those who did not take glucocorticoids weighed a mean 74.2 and 82.3 kg, respectively. Both groups experienced a similar, large mean improvement in Disease Activity Score.

After 4 weeks of therapy, BMI rose in 41% of patients who took a glucocorticoid versus 32% of those who did not (difference not statistically significant). Fifty-five percent of glucocorticoid users experienced an increase in BMI by 12 weeks versus 23% of nonusers (P = 0.025). Disease Activity Score 44 did not differ statistically significantly between the two groups, either at baseline or after 12 weeks.

Dr Turk concluded that, after 12 weeks of therapy, patients with early rheumatoid arthritis who took methotrexate and glucocorticoids experience an increase in BMI more often than those who took methotrexate alone.

The difference in weight gain between patients who took versus did not take glucocorticoids was caused not by a difference in disease activity, but by changes in body composition induced by glucocorticoids. Weight gain in these patients needs further investigation over a longer period.

"After the analysis," Dr Turk said, "I concluded that many patients with rheumatoid arthritis gain weight, but patients taking glucocorticoids gain weight more often than those who don't take them."

She added, "We hope to perform larger studies including more patients and to scan patients with dual-energy x-ray absorptiometry. This will enable us to measure not only total weight, but also specific indices, such as fat mass and fat-free mass and fat distribution." ■

Biologic use for RA may reduce disease activity and disability

Exposure to biologics for longer periods has been linked to reduced disability and disease activity in a longitudinal retrospective study of patients with rheumatoid arthritis.

Nancy Ann Shadick, MD, MPH, of Brigham and Women's Hospital, Boston, Massachusetts, explained that biologics are now the standard of care for moderate to severe rheumatoid arthritis in patients who responded inadequately to nonbiologic disease-modifying antirheumatic drugs. Though biologics are demonstrated to be effective in managing symptoms and disease activity, their long-term impact on disability has not been clarified.

> "We plan to look at the impact of methotrexate given alongside a biologic on these outcomes. We'd like to see how biologic therapy impacts ongoing radiographic progression in longstanding rheumatoid arthritis.

Dr Shadick remarked, "Limiting the long-term functional impairment that can occur in rheumatoid arthritis is a crucial goal".

She added, "Though biologics are known to improve symptoms and disease activity of rheumatoid arthritis, we also need to understand the long-term effects of biologics on functioning in patients with disease of longer duration."

Dr Shadick and investigators examined the link between patient disability due to rheumatoid arthritis and biologic exposure using longitudinal data from a group of patients with rheumatoid arthritis at an academic medical centre.

The team used linear mixed repeated measures regression to model the impact of biologic exposure on changes in disease activity (Disease Activity Score 28 C-reactive protein) and disability (modified Health Assessment Questionnaire).

At each follow-up visit, biologic exposure was calculated as the ratio of a patient's time on a biologic relative to duration of participation in the cohort. To identify predictors of disease activity and disability at the population level, yearly biologic exposure, outcome scores, and associated covariates were incorporated over a period of up to 13 years into the longitudinal regression models.

A total of 1395 patients with rheumatoid arthritis, 82.2% women, including 6783 physician visits from 2003 to 2015, were reviewed. At enrolment, patients had rheumatoid arthritis for an average of 12.7 years. Longer biologic exposure was linked to a significant reduction in annual population means for disability and disease activity ($P < 0.0001$).

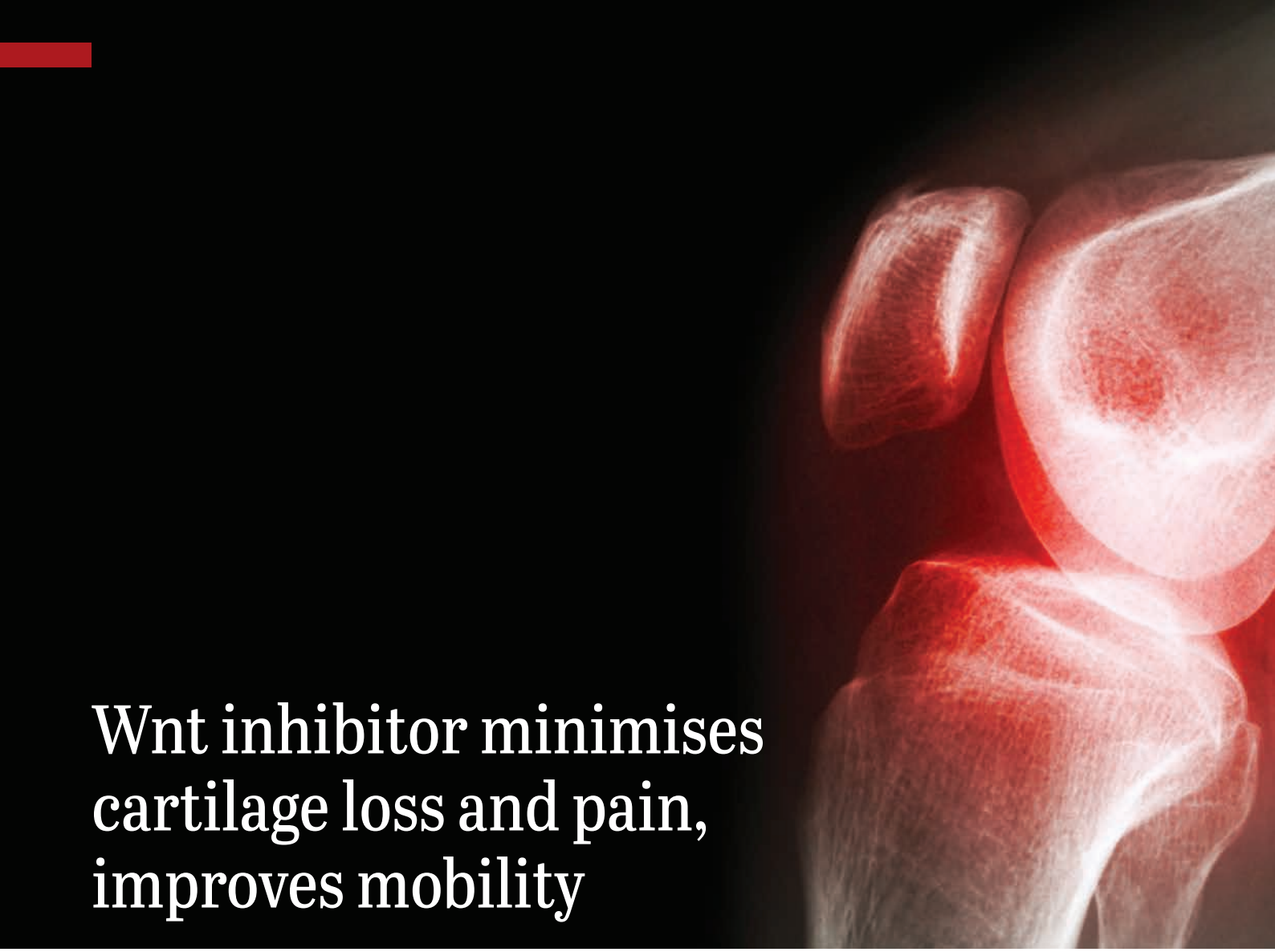
Disease Activity Score 28 or modified Health Assessment Questionnaire score at enrolment was the strongest predictor of disease activity and disability, respectively ($P < 0.0001$). Shorter disease duration ($P < 0.0001$), not using a biologic at enrolment ($P < 0.0001$), and methotrexate use ($P < 0.0003$) were significant predictors of reduced disability and disease activity.

Dr Shadick concluded that longer exposure to biologics was linked to reduced disease activity and disability in this longitudinal study of patients with rheumatoid arthritis. Biologic use improves functional status, but the status of rheumatoid arthritis at enrolment is still the most significant predictor of disability.

The results suggest that biologic use may reduce long-term disease activity and disability in patients with rheumatoid arthritis.

She continued, "Our study was drawn from data in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) registry, which is a real-world setting. It demonstrated that good outcomes, improved functional status, and reduced disease activity are evident in patients who stay on their biologic."

Dr Shadick added, "We plan to look at the impact of methotrexate given alongside a biologic on these outcomes. We'd like to see how biologic therapy impacts ongoing radiographic progression in longstanding rheumatoid arthritis, as well as to what extent reduced disability and disease activity affects cost-effectiveness."



Wnt inhibitor minimises cartilage loss and pain, improves mobility

A Wnt inhibitor showed early signs of minimising pain, improving joint mobility, and slowing or reversing cartilage loss in patients with osteoarthritis of the knee, according to positive results of a 24-week, multicentre, single-dose escalation, randomised controlled trial.

Yusuf Yazici, MD, of Samumed LLC, San Diego, California, explained that therapies for osteoarthritis treat joint pain and mobility, though they provide limited efficacy and their long-term safety is questioned. Recent research has demonstrated that the Wnt signalling pathway helps form joint tissues. The research has suggested that an altered Wnt pathway is linked to loss of cartilage.

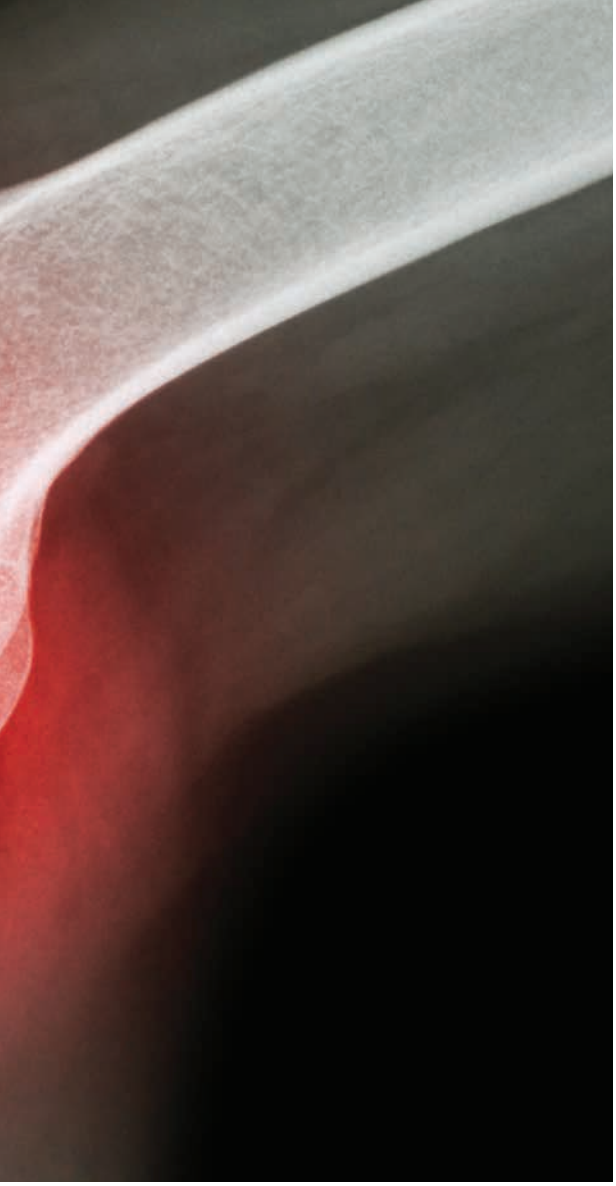
Dr Yazici remarked, "Osteoarthritis is debilitating and affects nearly 30 million patients in the US alone. We are looking to develop a disease-modifying therapy that regrows cartilage and also safely treats signs and symptoms of osteoarthritis."

Dr Yazici and coinvestigators assessed the impact of a single intraarticular injection of the Wnt inhibitor SM04690 on joint pain and mobility in 61 patients with moderate to severe osteoarthritis of the knee. They used Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) strict responder data to measure efficacy.

Dr Yazici commented, "We analysed OMERACT-OARSI responses to further evaluate the relevance of the data on signs and symptoms we had observed. SM04690 holds the potential of genuine disease modification, as well as alleviation of the signs and symptoms of osteoarthritis."

Patients were an average of 62.6 ± 5.7 years of age, 67% were female, and their average body mass index was 30.4 ± 4.7. Each escalation cohort of 20 patients included 16 patients given the study drug and four given placebo. SM04690 was dosed at 0.03, 0.07, and 0.23 mg in a 2 mL injection. Patients received one injection into the affected knee on the first day and were followed for 24 weeks.

Dr Yazici and colleagues collected safety, pharmacokinetic, biomarker, and preliminary efficacy data, including Western Ontario McMasters Universities Arthritis



Index (WOMAC Likert v3.1) measures. They evaluated the percentage of strict responders on OMERACT-OARSI in the modified intention-to-treat (mITT) population. Responders reported either WOMAC pain or function subscore improvement of ≥50%, coupled with a reduction in the given subscore of at least 20 points (0–100 scale).

Statistically significantly more OMERACT-OARSI strict responders were evident in the 0.07 mg cohort at week 12 versus placebo, 76% versus 36%, P = 0.04. Numerically, more of these responders were in the 0.03 mg cohort at week 24, 73% versus 36%, P = 0.07. More patients in the 0.07 mg cohort met both pain and functional criteria than those who received placebo at 12 and 24 weeks. Forty-four percent of patients in the 0.23 mg cohort responded at week 12 and 25% at week 24.

"SM04690 was shown to exert the potential for therapeutic effect on knee osteoarthritis pain and function versus placebo," Dr Yazici said.

He remarked, "More patients treated with a single, intraarticular injection of SM04690 than those who received placebo demonstrated a significant OMERACT-OARSI strict response, which is a composite score of clinical efficacy that requires both absolute and relative improvement. Through further analysis, we saw that the improvement in both pain and function drove the clinical response from baseline at 12 and at 24 weeks. Neither pain nor function measurement alone drove response. The dual improvement suggested clinically relevant, improvement in multiple dimensions of osteoarthritis."

Dr Yazici and his team also explored the potential ability of Wnt inhibitors to affect joint space narrowing and cartilage loss, two signs of worsening arthritis. "Treatment that can decrease not only pain but improve functioning in patients with osteoarthritis of the knee, and that can halt or reverse disease progression, would constitute a major advance in the treatment of osteoarthritis," he said.

To evaluate the change from baseline in joint space width (JSW) on x-rays, the investigators assessed the data further. They analysed JSW change using repeated measures analysis of covariance (ANCOVA). They adjusted for baseline JSW in the mITT population.

At 24 weeks, subjects in the mITT population who received 0.07 mg, exhibited a statistically significant increase in mean medial JSW of 0.49 ± 0.75 mm, P = 0.02, from baseline versus placebo. Mean medial JSW did not change in those who received 0.03 mg (mean 0.00 ± 0.69 mm). Mean medial JSW rose 0.15 ± 1.07 mm in the 0.23 mg cohort, and decreased 0.33 ± 0.87 mm in patients who received placebo.

Dr Yazici said, "The results, which were based on exploratory x-ray outcomes, suggest that SM04690 may help maintain or increase joint space width versus placebo."

"SM04690 provides a novel mechanism of action. Results to date suggest it is safe, and it holds the potential of disease modification, as well alleviation of signs and symptoms of osteoarthritis after a single injection. X-rays taken at baseline and 24 weeks after injection suggest that mean joint space width was maintained with a single dose, and increased with a second dose.

"Our next steps are to further evaluate the safety and efficacy of Wnt inhibitors. A phase 2 trial is being performed to that end, again, in patients with moderate to severe osteoarthritis of the knee.

"We hope SM04690 will continue to demonstrate safety and efficacy so the millions of patients with osteoarthritis of the knee will have a new treatment option available to them," he said. ■

"Improvement in both pain and function drove the clinical response from baseline at 12 and at 24 weeks. Neither pain nor function measurement alone drove response. The dual improvement suggested clinically relevant, improvement in multiple dimensions of osteoarthritis.

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References: 1. STELARA Product Information (15 August 2016). **2.** Pharmaceutical Benefits Scheme (PBS): STELARA listing. Available at: www.pbs.gov.au/browse/medicine-listing (accessed May 2016). **3.** Therapeutic Goods Administration. Australian Public Assessment Report for Ustekinumab (July 2015). **4.** Felquer ML, Soriano ER. *Curr Opin Rheumatol* 2015;27(2):99–106. **5.** McInnes IB *et al. Lancet* 2013;382(9894):780–789 [with supplementary material]. **6.** Kavanaugh A *et al. Arth Care & Res* 2015;67(12):1739–1749. **7.** Ritchlin C *et al. Ann Rheum Dis* 2014;73(6):990–999. **8.** Kavanaugh A *et al. Ann Rheum Dis* 2014;73(6):1000–1006. **9.** Papp KA *et al. Br J Dermatol* 2013;168(4):844–854. **10.** Papp KA *et al. J Drugs Dermatol* 2015;14(7):706–714.

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