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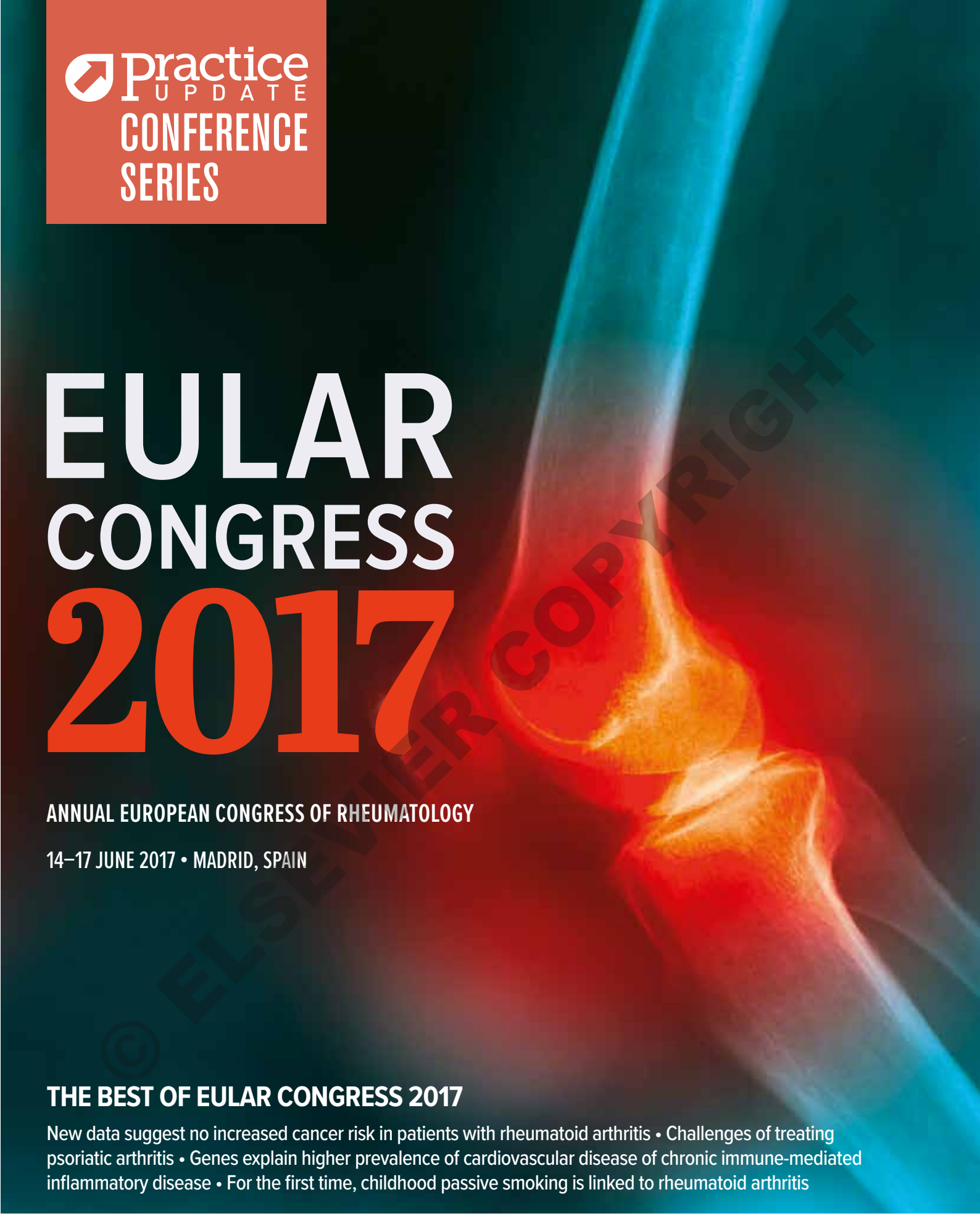

EULAR CONGRESS 2017

ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

14–17 JUNE 2017 • MADRID, SPAIN

THE BEST OF EULAR CONGRESS 2017

New data suggest no increased cancer risk in patients with rheumatoid arthritis • Challenges of treating psoriatic arthritis • Genes explain higher prevalence of cardiovascular disease of chronic immune-mediated inflammatory disease • For the first time, childhood passive smoking is linked to rheumatoid arthritis

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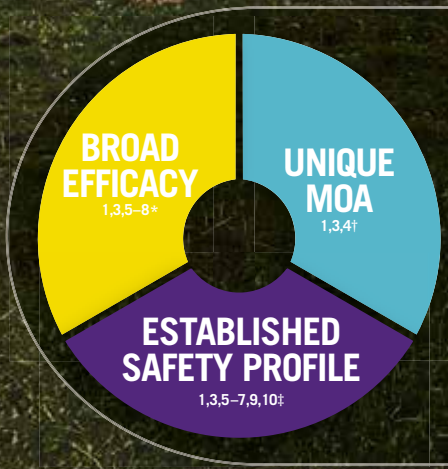
(ustekinumab)



A DIFFERENT APPROACH TO PsA[1,3,4†]

†First and only IL-12/23 inhibitor for the treatment of psoriatic arthritis

*Responses demonstrated across a range of psoriatic arthritis joint and skin symptoms, and disease activity through 2 years.

‡In both psoriatic arthritis and psoriasis patient populations.

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*Please note change(s) presented as **italicised text* in Product Information

References: 1. STELARA Product Information (27 February 2017). **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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ISSN 2208-150X (Print) • ISSN 2208-1518 (Online)

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475 Victoria Avenue Chatswood
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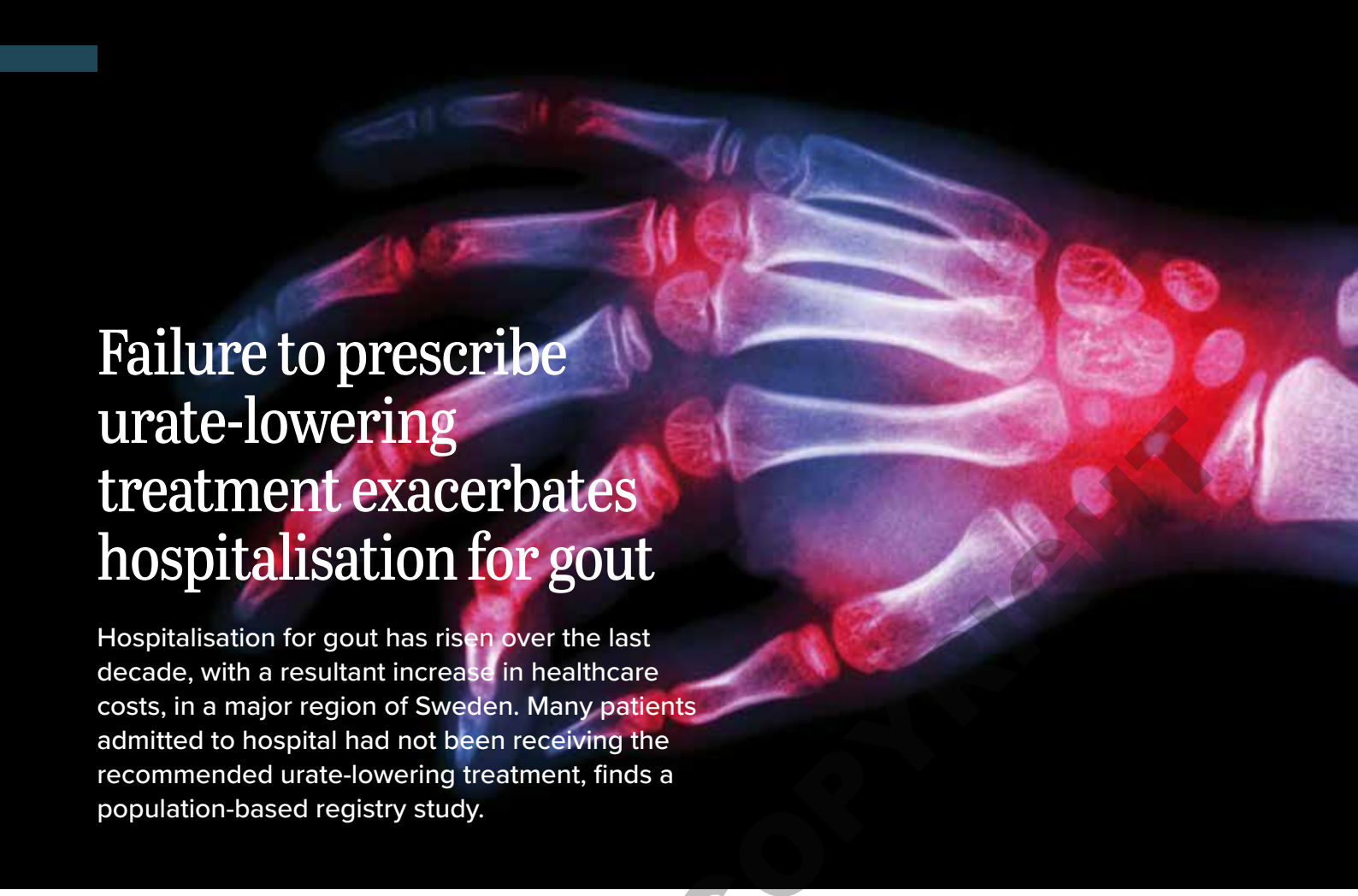


Failure to prescribe urate-lowering treatment exacerbates hospitalisation for gout

Hospitalisation for gout has risen over the last decade, with a resultant increase in healthcare costs, in a major region of Sweden. Many patients admitted to hospital had not been receiving the recommended urate-lowering treatment, finds a population-based registry study.

Dr Mats Dehlin

Mats Dehlin, MD, of the Sahlgrenska Academy at the University of Gothenburg, Sweden, explained that gout is the most common arthritic disease in the world, and incidence and prevalence are increasing. An increase in hospitalization for gout has been shown over the last two decades in North America.

"It is important to collect these data from different parts of the world as gout prevalence will vary as well as the course of the disease, due to cultural, ethnic and genetic factors," Dr Dehlin said.

Dr Dehlin and colleagues set out to assess hospitalization trends for gout using data from the healthcare consumption register from 2001 through 2012 in the Western Swedish Health Care Region, an area of the country believed to represent the whole of Sweden. Patients aged 18 years and older who were hospitalized during the study period with a principal ICD-10 diagnosis of gout at discharge were included.

Dr Dehlin and coinvestigators calculated annual population rates for hospitalization for gout. Inflation-adjusted healthcare costs for gout hospitalizations were calculated using the Cost-Per-Patient register. Dispensation of urate-lowering therapy, including allopurinol and probenecid, was identified using the Swedish Prescribed Drug Register within 6 months prior to hospitalization.

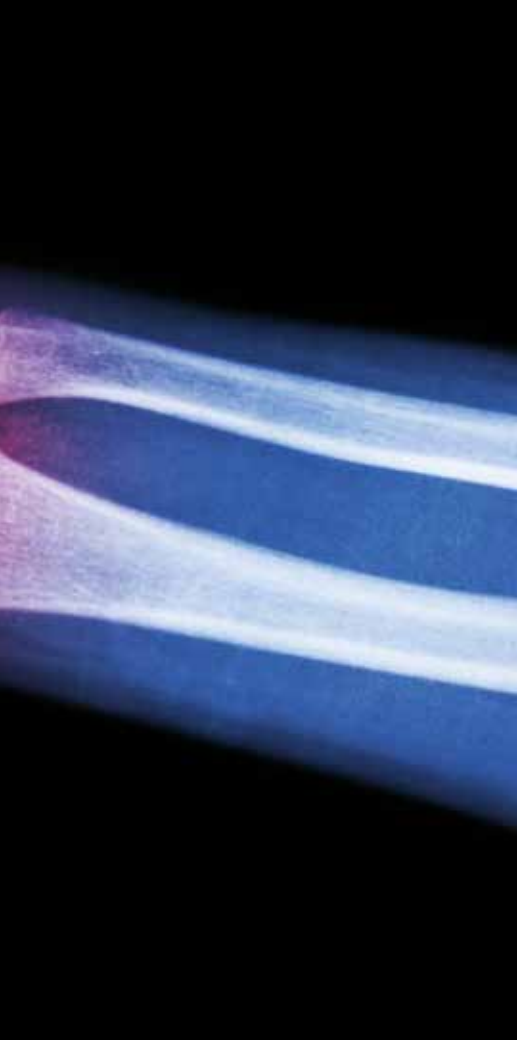
A total of 1873 hospitalizations for gout were recorded (mean patient age 75.0–77.6 years, 61–74% men) between 2000 and 2012. Demographic characteristics were similar over the study period.

From 2000 to 2012, the annual hospitalization rate for gout in western Sweden increased from 12.2 to 16.7 per 100,000 adults (P = 0.0038). This rise was most pronounced over the last 3 years of the study in males aged 65 years and older. In addition, the length of hospitalization increased from a median of 3 to 5 days in 2000 and 2012, respectively (P = 0.021). The increase was exacerbated by widespread failure to treat.

The findings are in marked contrast to the overall trend in hospitalization across the Western Swedish Health Care Region. Over the same decade, the number of days of inpatient care due to physical conditions in the region decreased by 9% from 2002 to 2012 (1,267,900 days, mean duration 5.7 vs 1,151,630 days, mean duration 4.9 days, respectively).

From 2009 to 2012, inflation-adjusted healthcare costs for gout hospitalization increased from $521,000 to $815,000. Only a minority of patients, 19% to 27%, received urate-lowering therapy in the 6 months preceding hospitalisation, with no obvious cyclical or seasonal trend.

Dr Dehlin concluded, "The incidence of hospitalization for primary gout has increased substantially in Sweden over the last decade, and this is reflected in associated healthcare costs. Though we would expect more hospitalizations due to the increasing incidence of gout among an aging population, the



problem is exacerbated by the fact that only one-fourth of hospitalized patients were taking the recommended urate-lowering therapy preceding admission."

UK experience: nurse-led vs GP-led care on patient outcomes

In a related study, nurse-led management of gout following treat-to-target principles improved patient outcomes significantly vs standard general practitioner care.

Michael Doherty, MD, PhD, of the University of Nottingham, UK, explained that gout results from urate crystal deposition in and around joints due to persistent elevation of uric acid levels above a critical level (saturation point). Gout is characterised clinically by recurrent attacks of acute inflammatory arthritis, irreversible joint damage and increased risk of cardiovascular disease, chronic kidney disease, and shortened life expectancy.

Gout is the only "curable" chronic arthritis, inasmuch as pathogenic urate crystals can be removed effectively using urate-lowering therapy, supported by lifestyle modifications to reduce modifiable risk factors. These may include weight loss if the patient is overweight or obese, reduction in excess dietary purines/fructose/alcohol, and alteration in antihypertensive and other drug treatments that elevate uric acid levels.

Dr Doherty and colleagues set out to compare nurse-led care vs care by a standard general practitioner of patients with gout. A total of 517 participants who suffered from acute gout in the previous year, identified from 56 local general practitioner practices, were randomized to care by a nurse or general practitioner in a 2-year controlled trial.

After receiving full information about gout, almost all participants in the nurse-led group requested urate-lowering therapy. Comparing the nurse and general practitioner groups at 2 years, 95% vs 29% achieved a target serum uric acid <360 µmoL/L, the primary outcome measure.

Eighty-eight percent vs 16% achieved a serum uric acid level <300 µmoL, respectively. Mean serum uric acid level was 252 ± 73 µmoL/L vs 418 ± 106 µmoL/L, respectively ($P < 0.001$ for all three measures).

In terms of patients in the nurse- and general practitioner led groups who were still receiving treatment at 2 years, 97% vs 54% were taking urate-lowering therapy. The mean allopurinol dose was 470 ± 140 vs 240 ± 107 mg daily, respectively ($P < 0.001$ for both measures).

Mean gout attack frequency during the second year was 0.33 ± 0.93 in the nurse-led vs 0.94 ± 2.03 in the general practitioner-led group ($P < 0.001$). After 2 years, tophi (deposits of crystalline uric acid and other substances on the joint surface or in skin or cartilage) were present in 2.6% (reduced from 13.7%) vs 9.6% (increased from 8.8%), respectively ($P < 0.02$).

Though equivalent at baseline, physical component score on the Short Form 36 health survey questionnaire among was significantly better among the nurse-led group at 2 years (mean 41.31 ± 16.76 vs 37.87 ± 14.31, $P < 0.05$).

"Patients in the nurse-led group did significantly better in terms of achieving their target uric acid level. Their adherence to urate-lowering therapy was excellent. Our findings confirmed the importance of patient education in the successful management of gout."

He continued, "The results reinforced the benefits of a treat-to-target strategy to achieve significant improvement in patient-centred outcomes such as the frequency of gout attacks, reduction in tophi and quality of life."

He added, "Compared to standard care from a general practitioner, adopting additional nurse support is likely to be cost-effective in the long term and merits further consideration."

Despite the increasing prevalence of gout in the UK, a variety of barriers result in suboptimal care, and only 40% of gout patients receive urate-lowering therapy, usually at a fixed dose without titration to a target serum uric acid level. Nurses manage many chronic diseases in the community successfully.

A previous preliminary proof of concept study in Nottingham had shown that, when people with gout are fully informed and involved in management decisions, uptake of urate-lowering therapy is high, and adherence after 1 year of nurse-led care is excellent. Dr Doherty's larger randomized controlled trial confirmed these findings over the 2-year period.

Nurses in Dr Doherty's study were trained in gout and its management according to recommended best practice (EULAR and British Society for Rheumatology guidelines), including providing full information, addressing illness perceptions and involving patients in management decisions.

Follow-up with a general practitioner was based on the usual standard of care. Assessments were undertaken after 1 and 2 years. Analysis was intention to treat with last observation carried forward.

The nurse-led (n=255) and general practitioner-led (n=262) patient groups were well matched at baseline for mean age (62 vs 64 years), sex (90% vs 89% men), mean disease duration (11.6 vs 12.7 years), mean gout attack frequency in the prior year (4.2 vs 3.8), the presence of tophi (13.7% vs 8.8%), mean serum uric acid (443 vs 439 µmoL/L), mean estimated glomerular filtration rate (71.5 vs 70.2) and use of urate-lowering therapy (40% vs 39%).

After 2 years, 22 (8.6%) vs 54 (20.6%) of participants had discontinued attending the nurse- and general practitioner-led groups ($P < 0.001$), including two vs eight deaths, respectively.

Dr Doherty concluded that the results showed that nurse-provided patient education and support for treat-to-target management of gout resulted in high uptake and excellent adherence to urate-lowering therapy over a 2-year period, with achievement of target serum uric acid in more than 90% of cases, and consequent improvements in patient-centred outcomes and quality of life. ■

New data suggest no increased cancer risk in patients with rheumatoid arthritis


Dr Johan Askling

Results of two retrospective reviews should reassure rheumatologists about the low risk of cancer from the use of biological disease modifying anti-rheumatic drugs (DMARDs), including anti-tumor necrosis factor (TNF) treatment, in patients with rheumatoid arthritis.

Johan Askling, MD, of the Karolinska Institute in Stockholm, Sweden, explained, "TNF is a cytokine involved in the immunosurveillance of tumors, so its inhibition may theoretically raise the risk of new tumor formation or cancer recurrence. Guidelines do not, however, provide clear direction regarding anti-TNF treatment in patients with recent malignancies."

Dr Askling and colleagues set out to investigate the risk of recurrence of solid non-skin cancer in patients with rheumatoid arthritis who were receiving anti-TNF treatment. A total of 446 patients with at least one diagnosis of solid cancer prior to the start of anti-TNF treatment were compared with 1278 matched controls with a history of equally recent cancer of the same type and stage who were not being prescribed biologic treatment.

Thirty individuals (7%) among these 446 patients with rheumatoid arthritis who were receiving anti-TNF treatment developed a cancer recurrence (crude incidence rate 14/1000 person-years) vs 89 (7%) among the 1278 matched biologic-naive controls (crude incidence rate 17/1000 person-years).

Statistical analysis accounted for matching variables: sex, birth year, year of diagnosis of the index cancer, and index cancer type and stage. Analysis adjusted for educational level and comorbidities indicated no increased risk associated with any specific cancer type, with the possible exception of uterine cancer, where the hazard ratio for recurrence was 14.8, but this was based on only one event among patients who were taking anti-TNF therapy.

Participants were required to be in cancer remission for 6 months prior to the start of follow-up. The primary outcome was first recurrence or second primary of the same cancer type, identified through the cancer registry through 2014.

Mean duration from index cancer diagnosis until anti-TNF treatment/start of follow-up was 9.9 and 9.5 years among patients treated with anti-TNF therapy and their matched biologic-naive controls, respectively. Mean follow-up from the start of anti-TNF treatment was 4.9 and 4.1 years, respectively.

The cancer stage distribution was similar between the two groups, apart from stage 4 (0.6% among anti-TNF treated patients and 1.6% among biologic-naive controls).

Previous nontuberculous mycobacterial infection raises risk of newly diagnosed Sjögren's syndrome

A link between newly diagnosed Sjögren's syndrome and previous infection with nontuberculous mycobacteria has been demonstrated in a nationwide, population-based case-control study.

Hsin-Hua Chen, MD, of the Taichung Veterans General Hospital in Taiwan, explained that Sjögren's syndrome is an immune-mediated chronic inflammatory disease in which the immune system attacks moisture-producing glands such as the tear and saliva glands. Inflammation within the glands reduces fluid production causing painful burning in the eyes, dry mouth and sometimes dryness in the nasal passages, throat, vagina and skin.

Primary Sjögren's syndrome occurs in patients with no other rheumatic disease; secondary Sjögren's syndrome occurs in patients with another rheumatic disease, most often lupus or rheumatoid arthritis.

The worldwide prevalence of primary Sjögren's syndrome has been estimated at approximately 0.2% of the adult population.

Sjögren's syndrome can affect patients of any age, though symptoms usually appear between the ages of 45 and 55 years. Sjögren's syndrome affects 10 times as many women as men. Approximately half of patients with Sjögren's syndrome also suffer from rheumatoid arthritis or other connective tissue diseases, such as lupus.

In this study, the diagnosis of nontuberculous mycobacteria was established using ICD9-Clinical Modification disease codes, as well as the prescription of antibacterial medication for nontuberculous mycobacteria. The association was quantified after adjusting for score on the Charlson comorbidity index and bronchiectasis.

Mean participant age was 55 ± 14 years and 87.8% of newly diagnosed cases of Sjögren's syndrome and controls without the disease were female.

An association was observed between nontuberculous mycobacteria infection (odds ratio 11.24; 95% confidence interval 2.37–53.24) and incident Sjögren's syndrome, but not between tuberculosis infection and incident Sjögren's syndrome (OR 1.29; 95% CI 0.97–1.71) after adjustment

Though guidelines caution against using anti-TNF drugs in individuals with a recent history of cancer (in the last 5–10 years), evidence of a lack of increased risk of cancer recurrence has been limited to women with breast cancer.

Data concerning anti-TNF treatment of rheumatoid arthritis and the risk of developing a new cancer, rather than a recurrence, have been largely reassuring.

In a second new study, overall cancer risk among patients with rheumatoid arthritis starting treatment with other biological DMARDs, including tocilizumab, abatacept and rituximab, as well as with a first- or second anti-TNF drug, did not differ substantially from that of patients with rheumatoid arthritis who were treated with conventional synthetic DMARDs.

Additional research will be required to exclude an increased risk of tumors at specific sites, or with longer latency.

Dr Askling concluded that the new data showed that, among patients with rheumatoid arthritis and a previous history of solid, non-skin cancer, those selected to receive anti-TNF treatment did not experience any more cancer recurrences than patients with rheumatoid arthritis who were treated with other classes of antirheumatic drug.

Also, the risk did not vary with timing of the start of anti-TNF therapy in relation to the original cancer diagnosis.

"Rheumatologists should find our data reassuring," he said, "though it is not possible to extrapolate these new findings to individuals with a very recent cancer or a poor prognosis."

Cancer risk of biological vs conventional synthetic DMARDs

In a related study, cancer risk was compared between biological and conventional synthetic DMARDs.

Hjalmar Wadström, MD, also of the Karolinska Institute, and colleagues, used Swedish national and population-based registers to assemble cohorts of patients with rheumatoid arthritis based on their first-time initiation of treatment, from 2006 through 2014, with one of the following biological DMARDs: tocilizumab, abatacept, rituximab or an anti-TNF treatment.

An additional cohort of patients initiated a second anti-TNF drug, and a cohort of biologic-naive patients with rheumatoid arthritis were treated with conventional synthetic DMARDs.

Outcomes monitored via the Swedish cancer registry were defined as a first-ever solid or hematological malignancy, excluding non-melanoma skin cancer, during follow-up. Patients with a previous malignancy were excluded. Patients were followed from treatment start until death, emigration, outcome, or the end of follow-up in December 2014.

Hazard ratios were calculated using a statistical model adjusted for age, sex, educational level, comorbidities, seropositivity, number of hospitalizations and days spent in inpatient care, use of prednisolone at baseline, use of nonsteroidal anti-inflammatory drugs at baseline, number of prescription drugs at baseline, and sick leave and disability the year before entry into the cohort.

Adjusting for age, sex, disease and treatment characteristics and educational level, no statistically significant differences were observed in risk of developing a first solid or hematological malignancy between patients initiated on tocilizumab, abatacept, rituximab or a first- or second anti-TNF drug and those treated with conventional synthetic DMARDs.

Dr Wadström concluded, "Immune suppression may lower a host's surveillance against developing tumors, so monitoring cancer incidence is an important aspect of the safety of biologics used in rheumatology."

He added, "Our data should be reassuring, bearing in mind the widespread use of anti-TNF drugs to treat rheumatoid arthritis. Though earlier reports concerning anti-TNF drugs and cancer risk in rheumatoid arthritis have been mostly reassuring, we knew a lot less about cancer risk with other biological DMARDs."

for score on the Charlson comorbidity index and bronchiectasis.

The magnitude of the association between nontuberculous mycobacteria and risk of Sjögren's syndrome was greatest among patients aged 45–65 years. No association was found between Sjögren's syndrome and previous tuberculosis infection.

Though an increased risk of tuberculosis has been found in patients with Sjögren's syndrome, in Dr Chen's study, tuberculosis infection itself did not appear to be associated with increased risk of developing Sjögren's syndrome.

Patients with no other rheumatic disease who were newly diagnosed with primary Sjögren's syndrome were approximately 11 times more likely to have been infected with nontuberculous mycobacteria than matched controls.

Dr Chen said, "Though the exact disease mechanism behind Sjögren's syndrome remains elusive, a variety of environmental, genetic and hormonal factors have been linked with the development and different manifestations of this debilitating disease. Identifying nontuberculous mycobacteria as a trigger may provide a clue to future development of a targeted therapy for these patients."

After excluding patients with Sjögren's syndrome who suffered from rheumatoid arthritis and systemic lupus erythematosus, an association was observed between nontuberculous mycobacteria infection (OR 11.24; 95% CI 2.37–53.24) and Sjögren's syndrome among 5751 newly diagnosed cases vs 86,265 patients without Sjögren's syndrome who were matched for age, sex and year of first diagnosis.

"Whether tuberculosis or nontuberculous mycobacteria infection is associated with the risk of Sjögren's syndrome is still unknown. Sjögren's syndrome is a disease of insidious onset, so we cannot exclude the possibility that it may have occurred before nontuberculous mycobacteria infection," Dr Chen said.

He continued, "Of the seven subjects with nontuberculous mycobacteria infection who were diagnosed later with Sjögren's syndrome, three were diagnosed within 3 months of nontuberculous mycobacteria infection, indicating the potential coexistence of these two diseases. The other four subjects, however, were diagnosed an average of 2.9 years after nontuberculous mycobacteria infection."

He added, "The significant association between nontuberculous mycobacteria infection and newly diagnosed Sjögren's syndrome supports the need to screen for Sjögren's syndrome in any patient infected previously with nontuberculous mycobacteria to enable prompt diagnosis and treatment."

Monoclonal antibody reduces spine fracture risk significantly in postmenopausal women with osteoporosis

Twelve months of treatment with romosozumab was associated with rapid and large reductions in vertebral fracture risk vs placebo in postmenopausal women with osteoporosis, reports the international, randomized, double-blind, placebo-controlled, parallel-group Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial.

Piet Geusens, MD, of Maastricht University in The Netherlands, explained that postmenopausal osteoporosis is considered a serious public health concern due to its high prevalence worldwide.

Approximately 30% of all postmenopausal women in Europe and the US are osteoporotic, and at least 40% of these women will sustain one or more fragility fractures in their lifetime.

The most common fractures associated with postmenopausal osteoporosis occur at the hip, spine and wrist. Vertebral and hip fractures are a particular concern. Vertebral fractures can result in intense back pain and deformity.

Romosozumab is a monoclonal antibody that binds and inhibits sclerostin, a glycoprotein produced by bone cells. This action exerts the dual effect of increasing bone formation and decreasing bone resorption, resulting in significant increases in bone mineral density.

Romosozumab, administered subcutaneously at monthly intervals over a 12-month period, has resulted in gains in both trabecular and cortical compartments of the spine and hip regions.

In Cosman et al, (*New England Journal of Medicine* 2016;375:1532-1543) significant increases in bone mineral density at 6 months reached 13.3% vs placebo in the spine. High-resolution quantitative computed tomography was used to evaluate trabecular and cortical components of the spine.

FRAME enrolled 7180 postmenopausal women, 55–85 years of age, with evidence of osteoporosis confirmed by abnormally low bone density scores in the spine, hip and femoral neck, but no severe vertebral fracture. Patients (n=3589) received a monthly dose of 210 mg romosozumab or placebo (n=3591) for 12 months.

Romosozumab was associated with a lower risk of new vertebral fractures than placebo at 12 months. The effect of romosozumab on the risk of vertebral fracture was rapid, with only two additional vertebral fractures to a total of 16 such fractures in the romosozumab group occurring in the second 6 months of therapy.

FRAME also evaluated romosuzumab treatment for 12 months followed by denosumab treatment for 12 months, vs placebo followed by denosumab treatment. Romosuzumab followed by denosumab was effective in reducing the risk of new vertebral fractures through 24 months.

In addition, clinical fracture (a composite endpoint that encompasses all symptomatic fractures, both nonvertebral and painful vertebral fractures) risk reduction, nonvertebral fracture (fractures outside of the spine, excluding sites not considered osteoporotic, fractures due to high trauma or pathologic fractures) risk reduction and other endpoints were assessed at 12 and 24 months.

After the placebo-controlled study period, patients entered the open-label phase where all patients received 60 mg denosumab subcutaneously every 6 months for 12 months, while remaining blinded to initial treatment. An additional 12-month extension period of open-label 60 mg denosumab subcutaneously every 6 months is ongoing.

Dr Geusens's new data from FRAME focused on the incidence of clinical vertebral fracture in women in the study who developed back pain consistent with this diagnosis. Monthly study visits in FRAME enabled timely confirmatory spinal X-ray.

Of 119 women who reported back pain over 12 months, 20 were diagnosed with new or worsening vertebral fracture. Three clinical vertebral fractures (<0.1% of patients and all in the first 2 months) occurred in the romosozumab group vs 17 (0.5%) in the placebo group.

Clinical vertebral fracture risk was 83% lower in the romosozumab group vs placebo at 12 months. In women with clinical vertebral fracture vs no clinical vertebral fracture, measurements of bone mineral density showed more severe osteoporosis.

Lumbar spine T-score was numerically lower and the Fracture Risk Assessment score higher at baseline. Other baseline characteristics were comparable, however, among women who reported back pain in both treatment groups.

Dr Geusens concluded that in women receiving romosozumab, all clinical vertebral fractures occurred during the first 2 months of treatment. Overall, the risk of a vertebral fracture was more than five times greater in the group of women given placebo.

Romosuzumab treatment for 12 months was associated with rapid and large reductions in clinical vertebral fracture risk vs placebo. Monthly study visits in FRAME allowed for timely radiologic confirmation of a suspected clinical vertebral fracture.

He said, "These results support this drug class as highly effective for postmenopausal women with osteoporosis with an established deficit in bone mineral density, who are at increased risk of fracture. The rapid and large reduction in clinical vertebral fracture risk is an important and highly relevant clinical outcome." ■

Early therapeutic intervention in patients with pre-rheumatoid arthritis reduces risk of rheumatoid arthritis significantly

Early therapeutic intervention in patients with so-called pre-rheumatoid arthritis reduces the risk of rheumatoid arthritis significantly in these patients after 52 weeks or more, report results of a meta-analysis.

Dr Bruno Fautrel

Bruno Fautrel, MD, of the Pitié Salpêtrière University Hospital in Paris, France, explained that recent progress in the understanding of the pathogenesis of rheumatoid arthritis has led to growing interest in the concept of pre-rheumatoid arthritis, defined as undifferentiated arthritis or very early rheumatoid arthritis, a clinical stage in which very early intervention could be efficacious.

Dr Fautrel and colleagues set out to evaluate very early therapeutic interventions in patients with pre-rheumatoid arthritis, that is, with either undifferentiated arthritis, or anticitrullinated protein antibody-positive arthralgia/arthritis (that is, very early rheumatoid arthritis) through a systematic literature review and meta-analysis.

> "Our data complements the newly launched EULAR campaign, "Don't Delay, Connect Today", which emphasises the importance of early intervention for patients with rheumatic and musculoskeletal diseases via early diagnosis and referral.

From 595 abstracts, nine randomized controlled trials (eight related to undifferentiated arthritis; one to very early rheumatoid arthritis) were deemed eligible for analysis, including two from congress abstracts.

Together these studies provided a total population of 1156 patients, with weighted mean age of 45.8 ± 15.2 years and mean symptom duration of 16.2 ± 12.6 weeks. A total of 66.0 ± 17.7% were female.

The main outcomes analyzed were rheumatoid arthritis occurrence at 52 weeks and beyond, and the absence of radiographic progression at week 52. The meta-analysis was performed using RevMan with Mantel-Haenszel method.

The systematic literature review followed Cochrane guidelines using the terms 'undifferentiated arthritis' or 'very early rheumatoid arthritis' associated with 'therapy' or 'treatment,' and was limited to randomized controlled trials published in English over the last 5 years.

In addition to searching PubMed, Embase and Cochrane databases, the review included EULAR and American College of Rheumatology congress abstracts from the past 2 years.

Two independent readers extracted data using a standardised form covering study quality, patient status at baseline, type of intervention and disease characteristics over time as well as the occurrence of rheumatoid arthritis.

The occurrence of rheumatoid arthritis at week 52 was available in six studies and at week 120 in one additional study (n=800). Early therapeutic intervention in these patients with pre-rheumatoid arthritis included methylprednisolone, methotrexate, tumor necrosis factor blocker, abatacept and rituximab. Outcome was assessed at week 52 for all studies except Van Dongen 2007 (PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment [PROMPT]), where it was assessed at week 120.

Early therapeutic intervention with methylprednisolone 80 to 120 mg IM, methotrexate, a tumor necrosis factor blocker, abatacept or rituximab reduced the risk of rheumatoid arthritis with a pooled odds ratio of 0.72 (95% CI 0.54–0.96), P = 0.02.

No statistically significant difference was observed between treatment vs placebo for the absence of radiographic progression (pooled odds ratio 1.36; 95% CI 0.82–2.27).

Dr Fautrel concluded that results of this meta-analysis demonstrated that early therapeutic intervention significantly reduces the risk of rheumatoid arthritis onset in patients with pre-rheumatoid arthritis. The benefit /risk balance and feasibility in clinical practice remain to be assessed further.

Dr Fautrel said, "Our review of available clinical data supports the rationale for early treatment in these patients. In studies where patients with pre-rheumatoid arthritis received active treatment, a significant reduction in the risk of rheumatoid arthritis was observed after 52 weeks or more. No statistically significant difference was observed, however, in the absence of disease progression as seen on X-rays between those taking active treatments vs placebo due to the early stage of disease."

He added, "Our data complements the newly launched EULAR campaign, "Don't Delay, Connect Today", which emphasises the importance of early intervention for patients with rheumatic and musculoskeletal diseases via early diagnosis and referral. The benefit/risk balance and feasibility of early aggressive treatment of pre-rheumatoid arthritis in clinical practice, however, still needs further assessment."

Over the past 15 years, knee and hip replacements and excess risk of cardiovascular events have dropped in patients with rheumatoid arthritis

Results of two studies have demonstrated that the incidence of total knee replacements carried out on patients with rheumatoid arthritis has begun to drop since the introduction of biological disease-modifying antirheumatic drugs (DMARDs) to Danish national treatment guidelines. Excess risk of cardiovascular disease has also declined in the population at large.


Dr Lene Dreyer


Dr Gaujoux-Viala

These conclusions were based on results of an interrupted time series analysis using nationwide Danish healthcare registries and a meta-analysis.

Total knee and hip replacement

Lene Dreyer, MD, of the Centre for Rheumatology and Spine Diseases, Gentofte in Copenhagen, Denmark, explained that Danish national guidelines recommending biological DMARD treatment for rheumatoid arthritis were introduced in Denmark in 2002.

In the present analysis, trends in the pre-biological DMARD guideline era (1996–2002) were compared with those in the biological DMARD period (2003–2016).

Five-year age and sex-standardised incidence rates of total hip and total knee replacement were calculated for 30,868 patients with rheumatoid arthritis who were diagnosed biannually between 1996 and 2011, vs 301,527 matched controls who did not suffer from rheumatoid arthritis.

Prior to 2002, when the updated guidance on biological DMARDs for rheumatoid arthritis was introduced, the incidence of total knee replacement had been increasing among patients with rheumatoid arthritis. In a general population of individuals matched in terms of age, sex and locale of residence, the incidence of total knee replacement continued to rise from 1996–2016.

In contrast, the incidence of total knee replacement in patients with rheumatoid arthritis began to drop after the introduction of biological DMARDs in Danish national treatment guidelines.

The incidence of total hip replacements has also maintained a steady rise in the matched population. Among patients with rheumatoid arthritis, however, apart from a surprising increase in 2003, the incidence of total hip replacement has trended downward both before and after the guidance was introduced.

Data are conflicted regarding the possible impact of more aggressive treatment, including biological DMARDs, on the need for knee and hip replacements in patients with rheumatoid arthritis.

With a baseline incidence rate of 5.87 total knee replacements per 1000 person-years in patients with rheumatoid arthritis, based on biannual data, before 2002, the incidence of total knee replacement had been increasing at a rate of +0.19 per year. After 2003, the downward trend has been equivalent to a –0.20 reduction in incidence per year.

With a baseline incidence rate of 8.72 total hip replacements per 1000 person years in patient with rheumatoid arthritis, based on biannual data, the downward trend was equivalent to a –0.38 reduction in incidence per year both before 2002 and after 2003. In 2003, the annual incidence of total hip replacement rose temporarily by +2.23.

Dr Dreyer said, “Our findings showed a clear downward trend in these two operations in Danish patients with rheumatoid arthritis since the addition of biological DMARDs to treatment protocols.”

“Also,” he added, “the overall pattern of our findings is in line with those recently reported from England and Wales. In addition, more widespread use of conventional DMARDs and the treat-to-target strategy may have contributed to this positive development.”

Excess risk of cardiovascular events

The excess risk of cardiovascular events in patients with rheumatoid arthritis relative to the general population has decreased since the year 2000.

Cécile Gaujoux-Viala, MD, of the University of Montpellier and the Nîmes University Hospital in France, explained that compared with the general population, patients with rheumatoid arthritis are known to be at increased risk of cardiovascular disease or events, including stroke, myocardial infarction, congestive heart failure and cardiovascular mortality.

Dr Gaujoux-Viala and colleagues set out to assess the excess risk of cardiovascular events in patients with rheumatoid arthritis vs the general population before and after the 2000s. They performed a detailed literature search that included PubMed and Cochrane Library until March 2016.

Of 5714 screened references, 28 eligible observational studies provided data on cardiovascular events (stroke, myocardial infarction, congestive heart failure, cardiovascular mortality) in patients with rheumatoid arthritis and in a control group.

The meta-analysis of relative risk concerning patients with rheumatoid arthritis in relation to the control group was performed for each cardiovascular event and for the periods before and after the 2000s.

For studies published before 2000, a highly significant increase in the risk of all four cardiovascular events was observed in patients with rheumatoid arthritis vs controls as follows:

- **Stroke**: relative risk 1.12, [95% CI 1.04–1.21, P = 0.002]
- **Congestive heart failure**: relative risk 1.25 [95% CI 1.14–1.37, P < 0.00001]
- **Cardiovascular mortality**: relative risk 1.21 [95% CI 1.15–1.26, P < 0.00001]
- **Myocardial infarction**: relative risk 1.32 [95% CI1.24–1.41, P < 0.00001]

In all studies published after 2000, increased cardiovascular risk was not related to congestive heart failure or cardiovascular mortality (relative risk 1.17 [95% CI 0.88–1.56], and relative risk 1.07 [0.74; 1.56], respectively).

Excess risk of myocardial infarction was reduced vs the period before 2000: relative risk 1.18 [95% CI 1.14–1.23], P < 0.00001. Excess risk of stroke remained stable (P = 0.006).

Dr Gaujoux-Viala concluded that the analysis confirmed the increased risk of cardiovascular disease among patients with rheumatoid arthritis relative to the general population. The excess risk appears, however, to be less prevalent than prior to the year 2000.

Coinvestigator Elisabeth Filhol, MD, of Nîmes University Hospital in France, said, "This reduction in cardiovascular risk may have two explanations. It may simply be due to better management of cardiovascular risk in patients with rheumatoid arthritis."

She continued, "Knowing that systemic inflammation is the cornerstone of both rheumatoid arthritis and atherosclerosis, it may also be related to better control of chronic systemic inflammation as the result of new therapeutic strategies."

Dr Gaujoux-Viala added, "Over the past 15 years, new treatment strategies such as tight control, treat to target, methotrexate optimisation and the use of biologic DMARDs have allowed better control of systemic inflammation in patients with rheumatoid arthritis." ■

High-sensitivity cardiac troponin T detects risk of stroke and MI in patients with lupus with no cardiovascular symptoms

High-sensitivity cardiac troponin T detected in the blood of lupus patients with no symptoms of cardiovascular disease and thought to be at low risk of cardiovascular disease based on traditional risk factors, has been associated with atherosclerosis, reports a prospective electrochemiluminescence series.

Karim Sacré, MD, PhD, of the Bichat Hospital in Paris, France, explained that systemic lupus erythematosus is a genetically complex chronic relapsing immune-mediated rheumatic disease characterised by inflammation that may affect tissues such as the skin, joint linings, lungs, kidneys and other organs.

Lupus affects women predominantly, 10 times more often than in men, and frequently starting at childbearing age. The disease is highly variable in presentation and outcome among individuals and across different ancestral groups.

Premature cardiovascular disease is much more common in young premenopausal women with lupus than in healthy women of a similar age. With the increased life expectancy of patients with lupus due to improved therapy, cardiovascular disease has emerged as a significant threat to their health, and is a major cause of death and ill health in these patients.

Traditional risk factors such as the Framingham score have underestimated the risk of cardiovascular disease in this population.

Dr Sacré and colleagues set out to determine whether serum high-sensitivity cardiac troponin T helps to identify patients with systemic lupus erythematosus at risk of cardiovascular disease.

They assessed the presence of carotid plaques by ultrasound in 63 consecutive patients with systemic lupus erythematosus who were asymptomatic for cardiovascular disease vs 18 controls.

Serum high-sensitivity cardiac troponin T concentration was measured using the electrochemiluminescence method. Factors associated with carotid plaques were identified and multivariate analysis performed.

Using vascular ultrasound, 23 of 63 (36.5%) consecutive patients with lupus were found to harbor signs of carotid plaques vs only 2 of 18 (11.1%) of controls.

Neither patients nor controls exhibited symptoms of cardiovascular disease and all scored low on the Framingham risk factor scale. Only age (P = 0.006) and lupus disease status (P = 0.017) were independently associated with the presence of carotid plaques.

The percentage of patients with lupus with carotid plaques who demonstrated detectable high-sensitivity cardiac troponin T was 87%. Only 42.5% of patients with lupus without plaques exhibited a detectable blood level of high-sensitivity cardiac troponin T (P < 0.001).

Conversely, 54.5% of patients with lupus with detectable high-sensitivity cardiac troponin T, but only 11.5% with an undetectable high-sensitivity cardiac troponin T harboured carotid plaque (P < 0.001).

In the multivariate analysis, only body mass index (P = 0.006) and high-sensitivity cardiac troponin T (P = 0.033) were statistically associated with carotid plaques in this cohort of patients with systemic lupus erythematosus.

Dr Sacé concluded that detectable high-sensitivity cardiac troponin T concentration was independently associated with subclinical atherosclerosis in asymptomatic patients with lupus at apparent low risk for cardiovascular disease according to traditional risk factors.

The results raise the possibility that this easily obtained biomarker is useful for more rigorous risk stratification and primary prevention of cardiovascular disease in patients with systemic lupus erythematosus.

The risk of harbouring carotid artery atherosclerotic plaques was increased by a factor of eight times in patients with lupus whose blood tested positive for high-sensitivity cardiac troponin T.

Dr Sacré said, "Results of our study raise the possibility that this easily measured biomarker could be introduced into clinical practice as a more reliable way to evaluate cardiovascular risk in patients with lupus. This in turn will enable more effective primary preventive measures such as treating high lipid levels."

He continued, "Before introducing this new biomarker into clinical practice, we are conducting further research to confirm our findings on a larger cohort of patients, with a longer follow-up period. And we are analysing not only carotid plaques, but also major cardiovascular events." ■

Challenges of treating psoriatic arthritis

Despite biological therapy, patients with psoriatic arthritis report pain, and comorbidities present additional barriers to successful treatment, conclude results of two studies.

Dr Philip Conaghan

Dr Lars Erik Kristensen

In the first study, analysis of real-world, patient-reported data showed that self-reported pain is common among patients with psoriatic arthritis despite treatment with biologic therapies. Severe pain was associated with greater impairment in health-related quality of life, physical function, ability to engage in activities and productivity at work.

In the second study, the presence of comorbidities in patients with psoriatic arthritis, such as cardiovascular diseases, diabetes and depression, was associated with higher baseline disease activity, increased risk of discontinuing anti-tumor necrosis factor (TNF) treatment and a reduced rate of clinical response.

Treatments for psoriatic arthritis need to provide fast, sustained pain relief

Philip Conaghan, MD, PhD, FRACP, FRCP, of the University of Leeds, UK, explained that patients with psoriatic arthritis receiving traditional biologic treatment (mainly anti-TNF) for ≥3 months completed questionnaires on their use of nonprescription pain medication, work status, health-related quality of life, impairment in physical function, as well as in work productivity and activity.

These standardised questionnaires were used to assess the impact of various levels of pain:

- Health-related quality of life (Short Form 36, EuroQol 5D)
- Impairment in physical function (Health Assessment Questionnaire Disability Index)
- Impairment in work productivity and activity (Work Productivity and Activity Impairment Questionnaire).

Data were obtained from 782 patients with psoriatic arthritis who were recruited by rheumatologists and dermatologists across 13 countries spanning the Americas, Asia Pacific, The European Union, Turkey and the Middle East.

Responses to the pain section of the Short Form 36 questionnaire, a 36-item, patient-reported health survey, showed that despite treatment, more than one-third (36.8%) were experiencing severe pain and under one-third (30%), moderate pain. More severe pain was associated with increased use of prescription nonsteroidal anti-inflammatory drugs ($P = 0.0026$) and opioids ($P = 0.0065$), as well as nonprescription pain medication ($P < 0.0001$).

Impairment in health-related quality of life increased as the severity of their pain increased. This was reflected in clinically and statistically significant differences in levels of pain severity ($P < 0.0001$) on scores on the nonpain Short Form 36 domains (physical functioning, general health, vitality, social functioning, physical, emotional and mental health).

Using a second questionnaire (EuroQol 5D) to assess the impact of residual pain on health-related quality of life, scores for mobility, self-care, usual activities and anxiety/depression also worsened significantly with a higher level of pain ($P < 0.0001$).

In addition, more severe pain in these patients with psoriatic arthritis was associated with greater disability, greater impairment in activities, impairment in work impairment, work missed and impairment while working (all $P < 0.0001$).

Among patients of working age (≤65 years), the likelihood of unemployment or retirement due to psoriatic arthritis was higher among patients who reported severe pain: 58.3% vs moderate and mild pain, in which the likelihood of unemployment or retirement due to the disease was 10.0% and 19.0%, respectively ($P < 0.0001$).

Dr Conaghan concluded, "The findings highlight the need for psoriatic arthritis treatments that provide sustained improvement in pain to reduce the impact

of the disease on daily life and on cost. We should also assess whether a given biologic therapy controls inflammation adequately and consider noninflammatory causes of joint pain."

Comorbidities impair treatment adherence and response

Lars Erik Kristensen, MD, of the Parker Institute, Copenhagen University Hospital, Denmark, explained that psoriatic arthritis is known to be associated with several severe comorbidities. Anti-TNF treatment is reported to fail in as many as half of patients with psoriatic arthritis.

"To improve the treatment of patients with psoriatic arthritis, it is essential to not only recognise and monitor any coexisting comorbidity, but also to understand the impact of any comorbidities on patient management. Without implementing effective treatment of comorbidities, patient outcomes will inevitably disappoint," Dr Kristensen explained.

From a population of 1750 Danish patients with psoriatic arthritis who were receiving treatment with their first TNF inhibitor, those who scored higher on the Charlson Comorbidity Index were found to exhibit statistically significantly higher measures of disease activity at baseline than patients without comorbidities.

Patients with psoriatic arthritis who scored ≥2 on the Charlson Comorbidity Index adhered to therapy significantly shorter than those who scored lower. Mean duration of adherence to treatment was 1.3, 2.2 and 2.6 years in those who scored ≥2, 1 and 0, respectively (P < 0.001).

Patients with psoriatic arthritis and coexisting depression and/or anxiety adhered to treatment significantly shorter than those without depression and/or anxiety (mean duration of adherence to treatment 2.4 vs 1.7 years, respectively P < 0.027).

Patients who scored ≥2 on the Charlson Comorbidity Index were at significantly higher risk of discontinuing anti-TNF treatment than those without comorbidities (P = 0.001).

A statistically significantly smaller proportion of patients who scored ≥2 on the Charlson Comorbidity Index achieved a good, or good-or-moderate clinical response as defined by EULAR criteria at 6 months than those without comorbidities (23% vs 41% and 47% vs 54% respectively).

"To improve the treatment of patients with psoriatic arthritis, it is essential to not only recognise and monitor any coexisting comorbidity, but also to understand the impact of any comorbidities on patient management. Without implementing effective treatment of comorbidities, patient outcomes will inevitably disappoint.

Psoriatic arthritis and comorbidities

Psoriatic arthritis, an inflammatory arthritis associated with psoriasis, causes joint pain and swelling and leads to joint damage and long-term disability. Psoriasis occurs in 1–3% of the population. The estimated prevalence of psoriatic arthritis among patients with psoriasis varies widely, from 6–42%, due to heterogeneity in study methods and a lack of widely accepted classification or diagnostic criteria.

Due to dual involvement of the skin and joints, patients with psoriatic arthritis experience further impairment, and consequently, lower quality of life than patients with psoriasis alone.

Psoriatic arthritis is associated with multiple comorbidities in addition to skin and joint involvement. These include metabolic syndrome (hyperlipidemia, hypertension, diabetes mellitus, and obesity); other autoimmune diseases (for example, inflammatory bowel disease) and lymphoma.

In addition, this burden of physical comorbidities, which increases with psoriasis severity and with the presence of severe psoriatic arthritis, raises mortality.

Dr Kristensen concluded that this population-based study showed that the presence of comorbidities is linked to the level of disease activity, and that the greater the number of comorbidities, the worse the impact on both treatment response and adherence to therapy.

Fluorescence optical imaging may help identify joint inflammation in children earlier and with greater confidence

Fluorescence optical imaging, used to visualise inflammation in arthritic joints, has been shown to be as effective as ultrasound with power Doppler at monitoring response to treatment in juvenile idiopathic arthritis.

Dr Gerd Horneff

Fluorescence optical imaging was also found to be more effective than ultrasound with power Doppler at detecting inflammation in the absence of symptoms and signs, reports an imaging study performed during the early, intermediate and late phases of juvenile idiopathic arthritis.

Gerd Horneff, MD, of the Asklepios Children's Clinic in Sankt Augustin, Germany, explained that juvenile idiopathic arthritis is a chronic, debilitating disease of childhood and adolescence in which arthritis persists for at least 6 weeks with onset before age 16 years. The polyarticular form involves more than four joints within the first 6 months.

The incidence of polyarticular juvenile idiopathic arthritis varies worldwide with a vast difference between different global regions as well as within individual countries. The incidence of juvenile idiopathic arthritis ranges from 0.83 per 100,000 children in Japan to 23 per 100,000 in Norway, with low rates in Asian populations and relatively higher frequencies in children of European descent. The rate of juvenile idiopathic arthritis is increasing.

Ultrasound with power Doppler is potentially limited in its ability to visualise highly detailed inflammatory changes in juvenile idiopathic arthritis, such as altered blood flow in tiny blood vessels and/or capillary leakage, especially in very small finger joints. Its operator dependency is another drawback.

In contrast, fluorescence optical imaging may provide greater information on the microcirculation in these joints. Also, fluorescence optical imaging is time-efficient and operator-independent. It can be performed by nurses or other nonmedically qualified personnel.

Dr Horneff said, "Accurate detection of inflamed joints is essential to both guide treatment decisions and assess treatment efficacy in patients with juvenile idiopathic arthritis."

He added, "Fluorescence optical imaging may be used in clinical practice to identify joint inflammation accurately, earlier and with greater confidence. It should be particularly useful in identifying children with clinically nonapparent joint inflammation of the hands and/or wrists who need to start antirheumatic drug treatment."

Of 37 patients with polyarticular juvenile idiopathic arthritis, 24 were started on methotrexate and 13 on a biologic for the first time (11 on etanercept, one on adalimumab and one on tocilizumab, respectively).

Low-dose CT scanning improves assessment of ankylosing spondylitis

Low-dose computed tomography has been shown to be more sensitive than conventional radiographs in monitoring disease progression of ankylosing spondylitis in the Sensitive Imaging of Axial Spondyloarthritis (SIAS) validation study.

Anoek de Koning, MD, of the Leiden University Medical Centre, The Netherlands, explained that ankylosing spondylitis is a painful, progressive and disabling form of arthritis caused by chronic spinal inflammation. The prevalence of ankylosing spondylitis varies globally, and is estimated at 23.8 per 10,000 in Europe and 31.9 per 10,000 in North America.

Dr de Koning said, "Standard-dose computed tomography is a sensitive method for assessing structural changes in the spine in patients with ankylosing spondylitis. Its clinical utility, however, has been limited due to its use of relatively high doses of ionising radiation."

Low-dose CT, using a newly developed scoring method to assess bone formation in patients with ankylosing spondylitis, has been shown to be reliable and sensitive, with good consistency between interpreters of the images.

Dr de Koning and colleagues set out to validate low-dose CT further by comparing its ability to demonstrate syndesmophyte formation and/or an increase in syndesmophyte size. Syndesmophytes are bony spurs arising from the vertebral body close to the vertebral endplate. They can lead to fusion of vertebrae.

To assess low-dose CT, syndesmophytes were scored in the coronal and sagittal planes for all "quadrants" per view, thus scoring eight "quadrants" per vertebral unit. Formation of new syndesmophytes, growth of existing syndesmophytes and the combination of both was calculated per quadrant.

Syndesmophytes were scored as absent (score 0), <50% of intervertebral disc height (score 1), ≥50% of intervertebral disc height but no bridging (score 2) or bridging the intervertebral disc height (score 3).

Clinical examination showed effective response to these treatments, with the percentage of affected joints in the hand and fingers reduced from 23.6% at baseline to 16.4% and 9.0% at weeks 12 and 24, respectively.

The Juvenile Arthritis Disease Activity Score is a composite tool recently developed to score disease activity. Measurements of disease activity also showed effective response, with a significant reduction in mean Juvenile Arthritis Disease Activity Score, from 17.7 at baseline to 12.2 at week 12 and 7.2 at week 24.

The percentages of patients achieving Juvenile Idiopathic Arthritis American College of Rheumatology 30/50/70/100 response rates at week 24 were 85%/73%/50%/27%, respectively.

Of six variables assessed in the Juvenile Idiopathic Arthritis American College of Rheumatology 30/50/70/100 (physician assessment, patient/parent assessment, number of active joints, number of joints with loss of motion, measure of physical function and laboratory measure of inflammation), at least three must improve by 50%, 70%, 90% and 100%, respectively, with no more than one of the six worsening by >30%.

Using ultrasound at baseline, week 12 and week 24, 19.4%, 16.1% and 11.5% of the wrist or finger joints showed effusion; 18.8%, 12.7% and 9.6% showed thickening of the joint lining and, with the power Doppler function, 6.9%, 1.8%, and 5% of joints showed hyperperfusion, all signs of inflammation. Overall, any sign of arthritis was detected by ultrasound with power Doppler in 24.5%, 19.2% and 17% of joints at baseline, week 12 and week 24 respectively.

Fluorescence optical images are interpreted in three phases: an early phase (phase 1) where the flow of dye into the blood vessels can indicate higher perfusion, an intermediate phase (phase 2) where the dye remains longer in a pathological than a normal vessel and a late phase (phase 3), where dye remaining in the tissues demonstrates more vessel formation due to chronic inflammation.

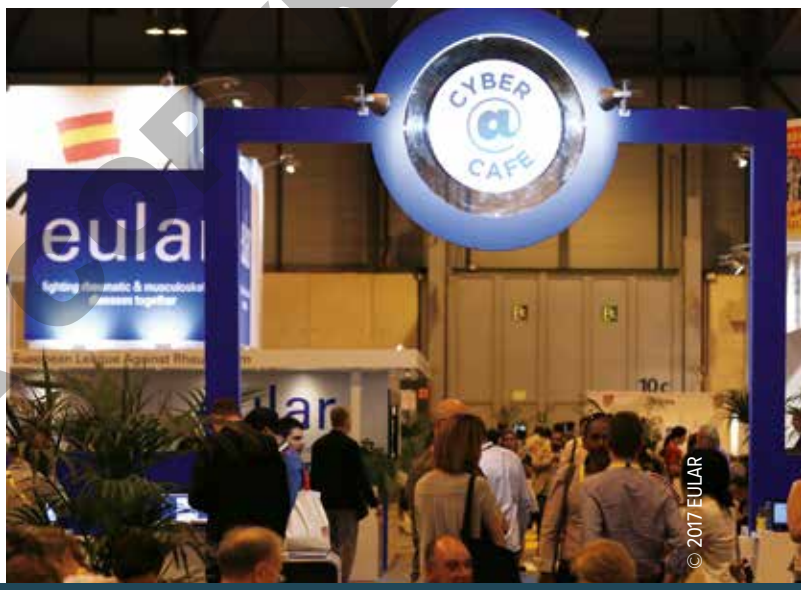
Among this patient population, fluorescence optical imaging showed signal enhancement, which suggested active inflammation in at least one phase in 38.7%, 29.2% and 27.6% of joints at baseline, week 12 and week 24 respectively.

Summarizing the data across all three time points, fluorescence optical imaging detected the highest number of signals suggesting active inflammation, with 32% of joints (especially in phase 2) vs 20.7% with ultrasound with power Doppler and 17.5% by clinical examination.

A high number of joints (21.1%) exhibited fluorescence optical imaging signals suggestive of inflammation but were clinically inactive. A total of 20.1% of joints that exhibited fluorescence optical imaging signals did not show effusion, synovial thickening or hyperperfusion on ultrasound with power Doppler.

Dr Horneff concluded, "Fluorescence optical imaging, with its ability to detect inflammation in joints not detected by clinical examination or ultrasound with power Doppler, will be helpful in guiding treatment decisions based on the number of affected joints."

He added, "Also, its discrimination between painful but uninflamed joints and those with inflammation will avoid unnecessary treatment with conventional disease-modifying antirheumatic drugs or biologics in the former."



Consensus regarding each of these outcomes was defined by agreement of both readers on the same vertebral level. Data were compared per reader and for the consensus score.

Patients were recruited from the Sensitive Imaging of Axial Spondyloarthritis (SIAS) cohort from Leiden, The Netherlands, and Herne, Germany. Fifty patients with ankylosing spondylitis were included based on:

- Modified New York criteria (classification criteria that include inflammatory back pain, limitation of lumbar spine movement, decreased chest expansion and structural damage of the sacroiliac joints on X-rays)
- The presence of one or more syndesmophytes on either the cervical and/or lumbar spine seen on X-ray
- One or more inflammatory lesions on an MRI of the entire spin.

Each patient underwent conventional X-ray of the lateral cervical and lumbar spine and low-dose CT of the entire spine at baseline and after 2 years. Two investigators assessed the images independently in separate sessions. Images were paired per patient, blinded to time order, patient information and the result of the other imaging technique.

Comparing the percentage of patients with newly formed syndesmophytes, growth of existing syndesmophytes and the combination of both, scored by two investigators and as a consensus score, low-dose CT detected more patients with progression in all comparisons. This was especially apparent where there was a higher number of new or growing syndesmophytes per patient.

Using the strictest comparison of the consensus score for both low-dose computed tomography and X-rays, 30% of patients exhibited newly formed or growth in bony proliferation at three or more sites with low-dose CT vs only 6% with conventional X-rays.

Dr de Koning concluded that low-dose CT was shown to detect more patients with ankylosing spondylitis with signs of disease progression, more consistently, than conventional X-rays.

Low-dose CT covering the entire spine is a more sensitive method to assess formation and growth of syndesmophytes than conventional radiography. The latter is limited to the cervical and lumbar spine in patients with ankylosing spondylitis.

"Our findings," she said, "support the use of low-dose CT as a sensitive method to assess new or growing syndesmophytes in clinical research without exposing patients to high doses of radiation."

Genes explain higher prevalence of cardiovascular disease of chronic immune-mediated inflammatory disease

Specific genetic loci previously identified as being associated with cardiovascular risk in the general population have been found to be significantly increased in association with cardiovascular risk among patients with chronic immune-mediated inflammatory disease. Four loci have been found to exert varying genetic effects across different chronic immune-mediated inflammatory diseases, reports a cross-phenotype genome-wide meta-analysis.

Antoni Julià Cano, PhD, of the Rheumatology Research Group, Vall d'Hebron Hospital in Barcelona, Spain, explained that autoimmune diseases are highly disabling chronic disorders characterised by activation of multiple immune and inflammatory pathways against self-components.

Patients with autoimmune diseases carry a higher prevalence of cardiovascular events than the general population. Understanding genetic and biological mechanisms underlying cardiovascular disease risk in autoimmunity could be fundamental to developing more efficient preventive and therapeutic strategies.

Dr Julià Cano and colleagues set out to characterise the genetic basis of cardiovascular disease risk in chronic immune-mediated inflammatory disease. They genetically profiled 6485 patients with one of six chronic immune-mediated inflammatory diseases: rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis.

Patients were recruited by the Spanish Biomedical Immune-Mediated Inflammatory Disease Consortium. All were Caucasian European from Spain. The presence of cardiovascular disease was defined as having suffered one or more of the following: ischaemic heart disease (myocardial infarct and angina), stroke and peripheral arterial disease.

First, the investigators tested the association of established cardiovascular risk variants within each autoimmune disease. Second, they analysed the association of autoimmune disease risk variants with an increase in cardiovascular disease risk. Finally, they used the cross-phenotype meta-analysis approach to perform a genome-wide meta-analysis and to identify global genetic patterns associated with cardiovascular risk in autoimmune diseases.

The application of genome-wide association studies has created a still growing set of genetic markers associated with increased risk for a multitude of different diseases. Between 2006 and 2013, a wave of genome-wide association studies identified more

Anti-TNF certolizumab pegol does not, or only negligibly, transfers across the placenta in pregnant women with rheumatoid arthritis

The anti-tumor necrosis factor (TNF) agent certolizumab pegol has shown no or negligible placental transfer from pregnant mothers with rheumatoid arthritis to the fetus, reports a pharmacokinetic study.

Dr Xavier Mariette

Xavier Mariette, MD, PhD, of the University Hospitals of Paris-Sud in France, explained that effective and safe treatments are needed for women affected by chronic active inflammatory diseases, such as rheumatoid arthritis.

Adequate disease control is crucial to ensure the best fetal and maternal health, and to reduce adverse pregnancy outcomes. Anti-TNF agents are an effective therapeutic option, but most cross the placenta and the class is often stopped during pregnancy.

The molecular structure of certolizumab pegol is free of a fragment crystallisable region, so unlike other anti-TNF agents, no active placental transfer occurs. Results suggest a developing baby is not exposed to a meaningful concentration of certolizumab in the uterus, which in turn suggests that continuation of this specific anti-TNF treatment throughout pregnancy might be safe.

Dr Mariette said, "For rheumatologists, the management of patients with rheumatoid arthritis who wish to become pregnant involves balancing the need to withdraw certain drugs, while keep in rheumatoid arthritis and spondyloarthritis but, because most cross the placenta, they are often stopped during pregnancy."

Using a highly sensitive assay to measure the potential level of placental transfer of certolizumab from mothers to infants accurately, certolizumab

than 8500 genome-wide-significant associations. Cross-phenotype associations are genetic loci that appear to harbour variants associated with multiple, sometimes seemingly distinct traits. Cross-phenotype associations have been identified in several disease areas including protein tyrosine phosphatase nonreceptor type 22 (PTPN22) for immune-related disorders such as rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus and type 1 diabetes.

The increase in cardiovascular events in patients with chronic immune-mediated inflammatory diseases is explained by a combination of accelerated atherosclerosis and endothelial dysfunction, with inflammation providing the central link.

Seventeen genetic loci previously identified as being associated with cardiovascular disease risk in the general population were found to be significantly associated with cardiovascular disease risk among the chronic patient groups with immune-mediated inflammatory disease ($P < 0.05$).

Of these, four of the loci were found to exert significantly different genetic effects across these diseases ($P < 0.05$). In addition, six genetic loci linked to chronic immune-mediated inflammatory disease risk were found to be associated with an increase in cardiovascular risk, for example, the risk gene for rheumatoid arthritis CFLAR-CASP8.

The cross-phenotype genome-wide meta-analysis identified a total of 10 genetic patterns significantly associated with cardiovascular disease risk in these diseases.

Two of these genetic patterns showed a highly significant association with cardiovascular disease risk in rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus.

Functional analysis of these two genetic patterns revealed their significant enrichment in key pathways related to the etiology of rheumatic diseases such as TNFα (FDR <0.05) and IFNγ (FDR < 0.05) cytokine pathways.

Dr Julià Cano said that the results represented an important step toward characterising the genetic basis of cardiovascular disease risk in chronic immune-mediated inflammatory disease.

He said, "Our research findings help explain the higher prevalence of cardiovascular events observed in patients with chronic immune-mediated inflammatory disease than in the general population."

He continued, "At this stage, our results are significant in better understanding the disease process. They could also carry clinical implications, however, since some of the associated biological pathways are targeted by current therapies for chronic immune-mediated inflammatory disease."

He added, "Gaining a better understanding of genetic mechanisms underlying cardiovascular disease risk in these patients could be fundamental to developing more efficient preventive and treatment strategies." ■

levels were <0.032 µg/mL, the lower limit of quantification of the assay, in 13 of 14 infant blood samples at birth.

Only one infant harboured a minimal certolizumab level of 0.042 µg/mL at birth (infant/mother plasma ratio 0.09%). None of the infants harboured quantifiable levels at weeks 4 and 8.

Only three of 15 umbilical cord blood samples taken at birth harboured quantifiable certolizumab levels (maximum 0.048 µg/mL). No anti-certolizumab antibodies were detected in mothers, umbilical cords or infants. Infants of certolizumab-exposed mothers demonstrated safety consistent with that of unexposed similar-age infants.

Active transfer of an anti-TNF drug across the placenta involves binding of its fragment crystallisable region to the neonatal fragment crystallisable receptor, which in turn may result in adverse foetal or neonatal effects.

In contrast to other anti-TNFs, certolizumab lacks this fragment crystallisable region. Ex vivo studies using a human placental transfer model have shown that this unique structure of certolizumab limits its transfer through the placenta to the fetus.

The Multicenter, Postmarketing Study Evaluating the Transfer of Cimzia from the Mother to the Infant Via the Placenta (CRIB) was a pharmacokinetic study of pregnant women (≥30 weeks gestation) who received a maintenance dose of certolizumab for an approved indication. The last dose of certolizumab was within 35 days of delivery.

Sixteen of 21 certolizumab-treated pregnant women screened entered the study. Blood samples were collected from the mothers, umbilical cords and infants at delivery, and from infants again 4 and 8 weeks post delivery.

Certolizumab concentration was measured using a sensitive, certolizumab-specific electrochemiluminescence immunoassay, with a lower limit of quantification of 0.032 µg/mL. This assay is 10 times more sensitive than the assay used in prior certolizumab pharmacokinetic studies.

Maternal certolizumab plasma levels at delivery were within the expected therapeutic range (median 24.4 [5.0–49.4] µg/mL).

Dr Mariette concluded, "Results of this study support continuation of certolizumab treatment during pregnancy when necessary by providing robust information for women who need to control their disease during pregnancy."

He cautioned, "Risks of typical adverse effects associated with anti-TNF treatment, such as infection or an immune reaction, which could affect the outcome of the pregnancy will continue, however." ■

For the first time, childhood passive smoking is linked to rheumatoid arthritis

Dr Raphaèle Seror

A link between active smoking and risk of rheumatoid arthritis was confirmed at EULAR 2017. It was also suggested for the first time that in smokers, exposure to tobacco early in life via passive smoking in childhood increased this risk significantly. Smoking was also shown to be associated with increased progression of spinal structural damage in patients with ankylosing spondylitis.

Raphaèle Seror, MD, of the University Hospitals of South Paris in France, explained that rheumatoid arthritis is the most common chronic inflammatory joint disease, affecting approximately 0.5–1% of the population and causing progressive joint destruction, disability and reduced life expectancy.

In recent years, many potential environmental factors have been associated with increased risk of rheumatoid arthritis, but smoking is the only one that has been extensively studied thus far.

Passive smoking in childhood increased risk of rheumatoid arthritis in adult smokers significantly

Dr Seror and colleagues set out to assess the impact of active and passive smoking on the risk of developing rheumatoid arthritis. They tracked a large population of female volunteers born between 1925 and 1950 prospectively followed since 1990.

Eleven self-administered questionnaires were sent to participants between 1990 and 2014 to collect medical, demographic, environmental and hormonal data and dietary habits. The diagnosis of rheumatoid arthritis was collected in two successive questionnaires.

Cases were considered certain if, having been diagnosed with rheumatoid arthritis, they had taken a rheumatoid arthritis-specific medication such as methotrexate, leflunomide or a biologic since 2004 (the period from which drug reimbursement data was available). Women were excluded if they suffered from an inflammatory bowel disease and/or provided no information on smoking status.

Passive smoking was assessed by the question, "When you were a child, did you stay in a smoky room?" Patients were considered to have been exposed if the answer was "Yes, a few hours daily" or "Yes, several hours daily."

The usual intestinal transit, reported by women prior to a diagnosis of rheumatoid arthritis (average 10 years), was classified as normal transit, chronic diarrhea, chronic constipation and alternating between diarrhea and constipation.

Passive smoking exposure during childhood raised the association between risk of rheumatoid arthritis and adult active smoking. In smokers who experienced childhood passive exposure to smoke, the hazard ratio (HR) was 1.73 vs nonsmokers not exposed during childhood. In contrast, the HR was 1.37 in active smokers not exposed to passive smoke during childhood.

Of 70,598 women, 1239 self-reported suffering from rheumatoid arthritis, 350 who were eligible for analysis of the link to active and passive smoking, and 280 in the analysis of the link to a history of an intestinal transit disorder. Mean age at inclusion was 49.0 years, and mean duration of follow-up, 21.2 years.

Dr Seror concluded, "Our study highlighted the importance of avoiding any tobacco environment in children, especially in those with a family history of rheumatoid arthritis."

In the separate analysis seeking a potential association between the development of rheumatoid arthritis and a history of disrupted bowel function, previous chronic diarrhea was associated with more than double the risk of rheumatoid arthritis (HR 2.32), while chronic constipation or alternating between diarrhea and constipation did not impact risk (HRs of 1.16 and 1.07 respectively).

"An association between a history of chronic diarrhea and the risk of developing rheumatoid arthritis supports the hypothesis of dysbiosis (bacterial imbalance in the gut) as a risk factor for the emergence of immune-mediated inflammatory disease," explained Dr Seror.

She continued, "These data fit perfectly with the preclinical scheme of rheumatoid arthritis, where an external event occurs at an early stage to promote the emergence of so-called autoimmunity, followed years later by clinical rheumatoid arthritis."

Smoking also accelerates disease progression in ankylosing spondylitis

Dr Seror explained that ankylosing spondylitis is a painful, progressive and disabling form of arthritis caused by chronic inflammation of the spinal joints. The prevalence of ankylosing spondylitis varies globally, and is estimated at 23.8 per 10,000 in Europe and 31.9 per 10,000 in North America.

Though ankylosing spondylitis is strongly associated with the genotype HLA-B27, not everyone who tests positive for the marker goes on to develop the disease. Smoking, among other risk factors, increases the risk of developing ankylosing spondylitis.

Dr Seror and colleagues set out to determine whether smoking is associated with more rapid spinal damage and disease progression seen on X-rays in patients with ankylosing spondylitis. They conducted a detailed review and meta-analysis of all relevant, available studies.

Combined data taken from eight eligible studies suggested a significant association between smoking and cumulative spinal structural damage (odds ratio 2.02). Data from studies investigating the association between smoking and disease progression on spinal X-rays reflected in the formation of new syndesmophytes (bony growths) and/or an increase in size of these syndesmophytes is still being assessed.

Coinvestigator Servet Akar, MD, of Izmir Katip Celebi University in Izmir, Turkey, said, "Smoking constitutes a major risk factor not only for disease susceptibility but also disease severity in patients with ankylosing spondylitis. Rheumatologists should work hard to encourage their patients with ankylosing spondylitis to quit smoking, since smoking can impact their future quality of life in a major way."

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*Please note changes in Product Information.

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

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