Almost 20 years have passed since the first annual European League Against Rheumatism (EULAR) Congress took place on the sunny shores of the French Riviera in Nice. Since then, much has changed. The event has grown immensely, both in terms of participants and the breadth of research on offer; technology has been increasingly integrated to create a fully interactive experience; and, of course, the field’s understanding of rheumatic conditions has improved dramatically. However, one thing remains the same: the passion and dedication for improving the lives of patients.

The 19th Annual EULAR Congress was hosted in Amsterdam, Netherlands, a city famous for its myriad of waterways that dissect and connect the historic capital. In a sense, this aspect of the city embodied one of the central themes of the congress itself: connectivity. This year saw the EULAR organisers celebrate an inaugural year’s success for the ‘Don’t Delay, Connect Today’ campaign, which aimed to raise awareness of rheumatic conditions to encourage earlier diagnosis for better outcomes. Part of this campaign involved an exhilarating bike ride across the Scottish Hebrides to spread knowledge to one of the most isolated areas of the UK, and a summary of this exciting expedition can be found in the following pages.

The opening ceremony itself saw the EULAR President, Prof. Johannes W. J. Bijlsma, speak on a variety of subjects, praising the scope of the event’s scientific programme and the success of the ‘Don’t Delay, Connect Today’ campaign, as well as setting out the impressive goals for the coming years, primarily centred around education. “Education is one of the most important things we are working on. We made a nice text for the formulation of this goal: By 2023, EULAR will be (or stay) the leading provider of education in rheumatic and musculoskeletal disease.” When asked if this goal will result in the EULAR Congress’s evolution, Prof Bijlsma reiterated the intention of the event’s
organisers to always improve the congress year after year, striving to create the most dynamic programme and the best environment for the sharing of rheumatological data.

As well as looking to the future, the EULAR Congress, as ever, was a wonderful opportunity for the rheumatology community to revel in the successes of their peers. A huge array of abstract awards were presented, with each of the winners receiving €1,000; six winners were chosen for both basic and clinical research, three for the best Health Professionals in Rheumatology abstracts, and one for the best People with Arthritis/Rheumatism in Europe (PARE) abstract. As always, the EULAR Congress featured a strong focus on nurturing the next generation of rheumatologists and this was directly reflected in the awards ceremonies, with three medical students recognised for exceptional research.

This was a record-breaking year for the EULAR organisers in many ways, with 14,000 delegates in attendance from >120 countries and >5,050 abstract submissions. It speaks for the quality of research available in this field that >50% of those abstracts submitted were accepted for presentation and around 30% for publication; the finest 370 were hand-selected for oral presentation. The programme itself was vast, featuring >175 sessions, from expert-led symposia to hands-on workshops, and >560 speakers. While the sheer scale of this meeting could easily be intimidating, the popular What is New/How to Treat (WIN/HOT) track ensured that all delegates had quick and easy access to key sessions. Much of the fantastic research presented at this congress is recorded in the following pages in the form of Congress Highlights for you to enjoy. Whether you attended the congress and would like to refresh your memory, or are seeing the data for the first time, these highlights will surely get the creative juices flowing.

"By 2023, EULAR will be (or stay) the leading provider of education in rheumatic and musculoskeletal disease."
Comparison of Malignancy Rates Between Tocilizumab and TNF Inhibitors

CURRENT UNCERTAINTY surrounding the influence of biologic disease-modifying antirheumatic drugs (bDMARD) was the subject of one of the studies presented at the EULAR Congress. This study, which was reported in a EULAR press release dated 13th June 2018, compared tocilizumab (TCZ) to TNF inhibitors (TNFi) with regard to rates of malignancy, excluding nonmelanoma skin cancer, in patients with rheumatoid arthritis.

“With more biologic treatment options available and earlier initiation of therapy, it is important to understand the risk of malignancies in patients with rheumatoid arthritis.”

It is important to study malignancy rates in patients with rheumatoid arthritis because this patient group is at an increased risk of developing certain types of malignancies, which is thought to be due to chronic inflammation and/or immune dysregulation. It is critical to consider bDMARD in relation to malignancy rates, as, due to their target-specific inhibition of the immune system, there are concerns that bDMARD may increase malignancy rates, and existing data on this subject are conflicting. Therefore, as Prof Robert Landewe, Chairperson of the Scientific Programme Committee, EULAR, stated: “With more biologic treatment options available and earlier initiation of therapy, it is important to understand the risk of malignancies in patients with rheumatoid arthritis.”

With such a goal in mind, the researchers designed a study to compare TCZ to TNFi. Patients included in the study were adults with rheumatoid arthritis who had recently started either TCZ or TNFi treatment regimens after treatment failure on abatacept, tofacitinib, or another TNFi. Using three healthcare claims databases, the researchers matched the propensity score of 10,393 patients who received TCZ to 26,357 patients administered TNFi. The primary outcome of the study was incidence of malignancy, not including nonmelanoma skin cancer. Malignancy was determined based on two diagnostic codes within 2 months. Individual secondary endpoints were incidences of the 10 most frequently occurring cancers, leukaemia, and human papilloma virus-related cancer. It was found that there were no statistically significant differences between the treatment groups for either the primary outcome or the secondary outcome, providing valuable information for healthcare practitioners when they are considering therapeutic options for rheumatoid arthritis.

References
Intensive Treatment for Rheumatoid Arthritis Provides Long-Term Benefits

EARLY, intensive treatment of rheumatoid arthritis (RA) has been suggested to have long-term benefits for patients, including normalisation of mortality rates. According to a EULAR press release dated 13th June 2018, an avenue for the elusive improvement in RA patient mortality has been identified by a 23-year prospective study conducted by researchers at the VU University Medical Center, Amsterdam, Netherlands. Study author Prof Maarten Bowers, VU University Medical Center, commented on the novelty of the study: “Importantly, this study is one of the first to show a normalisation of RA mortality compared to the general population after 23 years of follow-up.”

The initial COBRA study1 included patients with early-stage RA who were randomised to receive either sulphasalazine (SSZ) monotherapy or SSZ in combination with low-dose methotrexate and initially high, step-down prednisolone. Combination therapy offered additional disease control compared to monotherapy. Follow-up 11 years later was carried out by another study and highlighted numerically lower mortality in patients receiving the combined therapy compared to the SSZ monotherapy; however, these results were not statistically significant.2

The study presented at the EULAR Congress included data from 154 of the original 155 patients, with a mean follow-up of 23 years. Results were compared with reference samples matched for age and sex. Again, a numerical lower mortality rate was found in the whole SSZ study population compared to the reference samples (28% and 35%, respectively). Within the study group, 27% of those randomised to the combined therapy died compared to 30% on SSZ monotherapy. However, neither of these results were statistically significant.

“...this study is one of the first to show a normalisation of RA mortality compared to the general population after 23 years of follow-up.”

Study author Prof Bowers commented on the results: “Our results confirm that early, intensive treatment of RA, including use of glucocorticoids, has long-term benefits.” Further studies are still warranted to elucidate a significant difference in mortality between mono and combined therapy; however, for the interim, these results are certainly encouraging and highlight a possible new therapeutic approach for those with this painful and debilitating disease.

References
Zoledronic Acid Treatment Shows Promise for Mild Osteoarthritis

KNEE OSTEOARTHRITIS patients did not show significant symptom improvements following 1-yearly infusion of zoledronic acid (ZA); however, ZA may give symptomatic relief to patients with milder disease. According to the results reported in a EULAR 2018 press release dated 13th June 2018, the treatment did not significantly reduce bone marrow lesion (BML) size or knee pain in the study participants over 2 years, but ZA was effective in nonradiographic osteoarthritis patients.

"...there may be a role for ZA to relieve symptoms in patients with mild osteoarthritis."

An age-related disease that affects >40 million Europeans, osteoarthritis has a substantial societal impact and economic burden, which is expected to become more significant in the near future as life expectancy increases. Since the therapeutic options for the disease are limited, research has focussed on drugs that effectively reduce the frequent symptoms of joint pain and BML.

A previous pilot study showed promising results for knee osteoarthritis patients after ZA infusion over 6 months; in a cohort of 59 adults, knee pain and BML size were both reduced following ZA treatment. A multicentre, randomised, double-blinded, placebo-controlled trial presented at the EULAR 2018 Congress therefore aimed to build on these successful results by showing that the symptomatic improvements could be reproduced over a 2-year period in a larger cohort of 223 patients. The study participants, who had a mean age of 62 years and a slight female predominance of 52%, had significant knee pain defined by a visual analogue score (VAS) ≥40 mm and MRI-detected knee BML.

The patients were randomised to receive either ZA or placebo once-yearly, but the results showed no significant changes in symptoms after 24 months. For example, for knee pain, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), scores were -37.5 versus -11.7 (p=0.205) and the VAS pain scores were -11.5 versus -16.8 (p=0.17) for the ZA and placebo groups, respectively. In addition, the knee BML sizes were -33.5 mm² versus 11.7 mm² (p=0.68) for the ZA and placebo patients, respectively.

However, ZA treatment of patients without radiographic osteoarthritis (joint space narrowing Grade 0) was more effective than placebo in prespecified analyses (WOMAC pain: -88.3 versus -42.6 [p=0.21]; VAS pain: -21.8 versus -8.3 [p=0.11]; and BML size: -67.4 mm² versus 98.2 mm² [p=0.14]). “It is disappointing that our results have not replicated the positive findings of the initial pilot study,” commented Prof Graeme Jones, Menzies Institute for Medical Research, Hobart, Australia, who added: “However, there may be a role for ZA to relieve symptoms in patients with mild osteoarthritis.”
Canakinumab Cuts Gout Flare Rates in Patients with Atherosclerosis

“OUR RESULTS demonstrate a striking effect of canakinumab on reducing the risk of gout attacks in atherosclerosis patients,” commented Prof Daniel Solomon, Harvard Medical School and Brigham and Women’s Hospital, Boston, Massachusetts, USA, speaking about the results of a secondary analysis of CANTOS trial data he was part of. These results were reported in a press release from the EULAR Congress, held from 13th–16th June 2018.

Gout is a very common condition; therefore, any insight that can be obtained, which may aid treatment, is of great utility. The researchers set out to examine the impact of canakinumab, enrolling 10,061 participants in the CANTOS trial. In the study, patients were randomised into four arms: placebo; 50 mg canakinumab; 150 mg canakinumab; and 300 mg canakinumab. All doses were given once every 3 months. Serum urate levels and high sensitivity C-reactive protein levels were initially measured and recorded at baseline and followed up every 3 months during the first year of the study. After the first year, measurements were taken annually. At baseline, gout status, determined by the physician’s diagnosis, was recorded, and any subsequent gout recurrences were noted during follow-up as a section of the systematic adverse event reporting.

“Our results demonstrate a striking effect of canakinumab on reducing the risk of gout attacks in atherosclerosis patients”

In this secondary analysis, the researchers divided the participants from the original study into three groups determined by baseline serum urate level: <6.9 mg/dL (low), 6.9–8.9 mg/dL (medium), and ≥9.0 mg/dL (high). One aspect of the analysis involved investigating the potential of serum urate as a biomarker. A correlation between baseline serum urate with gout flare and major cardiovascular event rates was found. The rates of gout flares per 100-person years were found to be 0.28, 1.36, and 5.94 for the low, medium, and high baseline serum urate groups, respectively. It should be noted that canakinumab did not influence serum urate levels; this result was expected, due to canakinumab’s mechanism of action.

A further aspect of the analysis was examining the impact of canakinumab on gout flare rates. The drug (in pooled doses) was found to significantly reduce gout flare rates across all baseline serum urate groups. Respective hazard ratios (95% confidence interval) for the low, medium, and high serum urate groups were 0.40 (0.22–0.73), 0.48 (0.31–0.74), and 0.45 (0.28–0.72), respectively. Prof Robert Landewé, Chairperson of the Scientific Committee, EULAR, commented: “These are significant results as they add to the evidence base demonstrating a potential preventative role for canakinumab in patients with gout.”

Lenabasum: Promising Treatment for Diffuse Cutaneous Systemic Sclerosis

LENABASUM has shown promising clinical results with acceptable safety in an open-label extension (OLE) of a Phase II study for the treatment of diffuse cutaneous systemic sclerosis (dcSSc). A EULAR press release dated 13th June 2018 reported these promising results, which are made even more astounding by the rarity of dcSSc, which affects just one of every four of the 30 people per million population per year diagnosed with systemic sclerosis (SSc).1

Lenabasum is a selective cannabinoid receptor type 2 agonist shown to reduce inflammation and fibrosis in animal models of SSc, and activates resolution of the innate immune response in humans. The drug was shown to cause changes in gene expression consistent with the biological effects of lenabasum on pathways relevant to SSc in a Phase II trial.2

Those patients who completed the Phase II trial (n=36) were enrolled into the 1-year OLE to receive 20 mg twice daily. Analysing the 25 patients who competed the OLE, an improvement in ACR CRISS score of 56% was observed along with a reduction in modified Rodnan Skin Score, HAQ-DI, Physician Global Assessment, and 5-D Itch Questionnaire by 8.6, 0.14, 0.9, and 2.3, respectively.
Mean duration of OLE treatment was 45 weeks, and 19 patients completed 60 weeks of treatment; three patients discontinued treatment, two due to adverse events (AE) and one withdrew consent. AE were reported in 33 of the 36 subjects, but only 7 were related to lenabasum, none of which were severe. Overall, 1 patient had AE considered life threatening, 3 patients had severe AE, 21 individuals had moderate AE, and 8 were mild. The most common AE from all subjects were upper respiratory tract infections (22%), urinary tract infections (14%), diarrhoea (11%), skin ulcers (11%), and mild intermediate dizziness (8%).

“Our results are very encouraging and reinforce the positive findings from the double-blind placebo-controlled part of the study with regard to safety and tolerability,” commented the principal investigator, Dr Robert Spiera, Director of the Scleroderma and Vasculitis Program, Hospital for Special Surgery, Weill Cornell Medical College, New York City, New York, USA. “We look forward to continuing our investigation to assess the role of lenabasum as a new treatment option for patients with dcSSc.” To build on these promising results, an international Phase III clinical trial of lenabasum has begun and results are expected in the first half of 2020.

References

Predicting and Preventing the Onset of Rheumatoid Arthritis

MOLECULAR changes that occur in rheumatoid arthritis (RA)-risk individuals could support development of early interventions to predict and prevent onset of the disease. As reported in a EULAR 2018 press release dated 13th June 2018, the results of two studies provide insights into gene signatures and biomarkers of arthritis onset that could inform novel diagnostics.
Focussing on RA-risk individuals who have specific RA autoantibodies but no evidence of joint destruction, the first study used synovial tissue of the knee joint and performed genome-wide transcriptional profile studies in 13 people. The resulting gene signatures were investigated using real-time PCR and showed that molecular changes appeared in the tissue before disease onset; a total of 3,151 transcripts were associated with a higher RA risk, including genes involved in several immune-response pathways. The analysis therefore successfully highlighted predictors of RA-risk individuals who will develop RA in the future, including positive glycoprotein 38 staining and lower lipid staining, enabling better understanding of the preclinical phase of the disease and suggesting novel drug intervention targets.

“These studies may help us better understand and potentially identify which individuals classified as at-risk will go on to develop RA”

The second study of individuals at risk of RA aimed to validate that B cell receptor (BCR) clones in the blood are a predictor of disease onset. According to the results, out of 129 participants, 45 had ≥5 dominant BCR clones, while the remaining were considered BCR-negative. After 104 months follow-up, 76% of the BCR-positive individuals developed RA compared to 13% of the BCR-negative cohort, equating to a relative risk of 5.8 (95% confidence interval: 3.2–10.3; p<0.0001). Further subanalyses showed that the number of dominant BCR clones significantly correlated with the risk of arthritis; for example, having ≥10 dominant BCR clones had a predictive value of 94% within 3 years. With a better predictive power compared to other available biomarkers, BCR clones could help clinicians predict imminent onset of RA in at-risk patients.

Since the structural joint damage associated with RA is irreversible, early recognition and treatment is vital to control disease progression. “These studies may help us better understand and potentially identify which individuals classified as at-risk will go on to develop RA,” commented Prof Robert Landewé, University of Amsterdam, Amsterdam, Netherlands. He added: “This is important because it will contribute to the development of early preventative strategies, including potential pharmacological treatment to prevent onset of disease.”

Significant Drop in Number of Joint Replacements

A DRAMATIC fall in the number of joint replacement procedures taking place in rheumatoid arthritis (RA) patients was highlighted by the results of a study reported in a EULAR press release, dated 13th June 2018. While the current scientific literature provides inconsistent evidence on the subject, one of the study authors, Dr John Hanly, Professor of Medicine (Rheumatology) and Pathology, Dalhousie University, Halifax, Canada, declared: “However, our results add significant evidence to show a clear reduction in joint replacement surgery in RA patients, most likely due to improvements in medical management over the last few decades.”
The researchers conducted a retrospective cohort study. Healthcare administration data from 1997–2010 was used to match patients with RA by age and sex to randomly selected controls in a 1:4 ratio. Over the course of the study, the mean age of individuals in the cohort increased from 56.7 to 60.1 years. Furthermore, the proportion of females increased from 70.8% to 73.9%.

"...our results add significant evidence to show a clear reduction in joint replacement surgery in RA patients..."

Overall, there was a 51.9% reduction in the number of joint replacement surgeries in patients with RA surgeries over the study period. It was noted that, by comparison, the number of joint replacements in the matched control group increased by 31.9% (p=0.002) during the same time period; however, the number remained less than that seen in the RA patient group. The researchers also examined the rates of cardiac interventions in an attempt to discern whether changes observed in joint replacement surgery were as a result of access to surgical procedures or improvements in RA therapy. It was found that rates of cardiac interventions did not show a significant change in either study group across the time period, suggesting the latter explanation.

This finding represented exciting news for rheumatologists, with Prof Robert Landewé, Chairperson of the Scientific Programme Committee, EULAR, proclaiming: “We welcome these results demonstrating such a dramatic reduction of joint replacements in RA patients in recent years.”

Cardiovascular Risk Linked to Pain Management Drug for Osteoarthritis

CARDIOVASCULAR risk in osteoarthritis (OA) patients has been linked to the cornerstone of OA pain management: nonsteroidal anti-inflammatory drugs (NSAID). Recent research has suggested OA is an independent risk factor for cardiovascular disease (CVD) and, according to a EULAR press release dated 13th June 2018, over two-thirds of the increased cardiovascular risk associated with OS is linked to NSAID use.

This pioneering longitudinal study evaluated the role of NSAID use in the development of CVD in 7,743 OA patients. Results showed OA patients had a 23% higher risk of developing CVD; the risk of congestive heart failure, ischaemic heart disease, and stroke all increased by 42%, 17%, 14%, respectively, in OA patients compared to the study’s 23,229 non-OA controls matched for age and sex. Researchers then assessed these results in relation to NSAID use: 68% of the total effect of OA on CVD risk was caused by NSAID. Congestive heart failure risk due to NSAID was 45% and >90% for ischaemic heart disease and stroke.

“Our results indicate that OA is an independent risk factor for CVD and suggests a substantial proportion of the increased risk is due to the use of NSAID.”

Prof Thomas Dörner, Chairperson of the Abstract Selection Committee, EULAR, explained why the link between cardiovascular risk and OA is an important area of study: “The examination
of cardiovascular risk among individuals with osteoarthritis is an important area of research as very little is known about the association, despite OA being the most common rheumatic disease with high prevalence among the elderly.”

Study author Prof Aslam Anis, School of Population and Public Health, University of British Columbia, Vancouver, Canada, summarised the study results: “Our results indicate that OA is an independent risk factor for CVD and suggests a substantial proportion of the increased risk is due to the use of NSAID. This is highly relevant because NSAID are some of the most commonly used drugs to manage pain in patients with OA.”

This study provides new information about the potential causal role NSAID play in the increased cardiovascular complications seen among individuals with OA. With these results there is no doubt that there needs to be further investigation into the effect that the widely prescribed NSAID can have on the cardiovascular health of OA patients.

The Youth-R-Coach Programme

EMPOWERING young people to become ‘experts-by-experience’, the Youth-R-Coach programme enables young people with chronic disease to share their personal experiences and support their peers. The details of this peer-to-peer programme were presented at the EULAR 2018 Congress and described in a EULAR press release dated 14th June 2018.

With the aim of increasing awareness of the millions of young people living with chronic rheumatic and musculoskeletal diseases across Europe, the Dutch project works with young people aged 18-27 years to create self-written books based on their own personal experiences. The work ranges from short columns to entire novels and is aimed at other young people, family members, teachers, and healthcare professionals to provide valuable insights into living with a chronic illness.

The programme involves groups of seven young people who take part in a kick-off meeting, a training weekend, and a final group workshop to share online coaching and presenting skills; however, the writing process is very much based on the individual person. To further provide participants with new coping tools and skills to teach others about the disease, each person is also given a mentor with a similar condition, with whom they communicate throughout the writing process.

“We have been amazed by the energy and enthusiasm of all the participants to share their experiences and act as a coach to their peers.”

Describing the great success of the project, Linda van Nieuwkoop, programme advisor and mentor for the Youth-R-Coach programme of Centrum Chronisch Ziek en Werk, Eindhoven, Netherlands, commented: “We have been amazed by the energy and enthusiasm of all the participants to share their experiences and act as a coach to their peers.” She added: “We are delighted with the diverse range of books that we hope will support other young people coping with a rheumatic or musculoskeletal disease, as well as other chronic conditions.”
This initiative supports Young PARE, a working group of the Standing Committee of PARE and part of EULAR, which works to establish and strengthen rheumatic and musculoskeletal disease youth groups across Europe and encourage the exchange of best practises throughout this network. Petra Balážová, Chair of Young PARE, expressed hope for international collaboration in the future following this initiative: “We hope that this will inspire other similar projects in other parts of the world.”

Continued Developments in the Use of Methotrexate

METHOTREXATE (MTX) was first approved for the treatment of rheumatoid arthritis (RA) 30 years ago. Since that approval, MTX has become established as the gold standard. During this time period, research on MTX has not stood still. A large number of new findings and developments have been presented over the years, enabling MTX therapy to become increasingly optimised. These new developments combined with therapeutic MTX optimisation were the subject of a symposium at the EULAR Congress, reported in a EULAR press release, dated 15th June 2018.

One way in which MTX therapy has been optimised is in regard to dosage and administration; it has been reported that higher doses of MTX and subcutaneous administration are more effective than the tablet form. Additionally, further studies have refined the subcutaneous administration method. As a result of its simpler handling, RA patients have been shown to prefer the Medac autoinjector over the pre-filled syringe. Such a finding is important, as utilisation of a preferred application method can have a major influence on patient compliance with therapy.

Throughout the course of the event, the benefits of continuing research into RA therapeutic options were emphasised.

MTX is also being examined from a gastroenterological perspective: through the prism of the microbiome. It is known that the expression of rheumatoid arthritis, and potentially the disease’s course, is influenced by the interaction between predisposed genetic factors and the microbiome. The influence of the microbiome on MTX is a topic of study. One piece of ongoing research has demonstrated that MTX has an inhibitory effect on the growth of different intestinal bacteria. Additionally, it is thought that the fact some species of bacteria can convert MTX into polyglutamated MTX might exert an influence on the efficacy of MTX therapy.

The symposium held at EULAR 2018 covered a variety of other topics, including MTX’s position in the treatment of juvenile idiopathic arthritis and MTX combination therapy. Throughout the course of the event, the benefits of continuing research into RA therapeutic options were emphasised.