



The EULAR 2018 Report

An authorised publication of the European League Against Rheumatism



Welcome to the EULAR 2018 Report

The Annual European Congress of Rheumatology 2018, hosted by the European League Against Rheumatism (EULAR), once again showed its recognition and appreciation as the prime platform for rheumatology



Prof. Bijlsma

information exchange and professional education in Europe and for the world. More than 14,700 attendees from 120 countries came to this year's EULAR Congress in Amsterdam to hear the best in rheumatology research and clinical advances. The scientific programme also included presentations carefully selected from more than 5,050 abstracts submitted.

The EULAR 2018 Report brings you highlights of some of the best presentations, focusing on the clinical and therapeutic findings that are able to change the way rheumatologists and other health professionals are practising medicine. We also report patients' insights. We hope that you will enjoy these accounts and statements of the latest in rheumatology clinical and translational research.

A number of the research reports that you will find in the EULAR 2018 Report also include access to video interviews with the presenters as well as other rheumatologists.

For details about the EULAR Congress, please visit www.congress.eular.org.

Best wishes and see you again 12-15 June in Madrid for EULAR 2019! □

*Prof. Johannes W.J. Bijlsma
President of EULAR
Professor of Rheumatology
Utrecht University, Netherlands*

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For patients not achieving treatment goals

RA PROGRESSION INTERRUPTED^{1,2}

Introducing **KEVZARA**—an IL-6 receptor inhibitor with the strength to interrupt RA progression in adult patients with moderately to severely active RA¹



KEVZARA[®]
(sarilumab) injection
200 mg | 150 mg

INDICATION

KEVZARA in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). KEVZARA can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.¹

KEVZARA has been shown to inhibit progression of joint damage and to improve physical function.¹

(▼) This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

SANOFI GENZYME 

Sanofi and Regeneron are collaborating in a global development program and commercialization for KEVZARA. © 2018 Sanofi. All Rights Reserved. 08/2018 SAGLB.SARI.17.06.0730a

Abbreviated prescribing information can be found on next page.

PREDICTABLE, FLEXIBLE DOSING

Every-2-week dosing¹

2 doses for dose reduction, if needed^{1*}

PATIENT CONVENIENCE

2 devices:
Prefilled syringe and
buttonless pen designed
for RA patients¹

2-week stability at
room temperature
(once removed from refrigeration)^{1†}

* Recommended dose is 200 mg every 2 weeks. KEVZARA can be down-dosed to 150 mg to help manage certain lab abnormalities associated with IL-6 pathway inhibition. Treatment with KEVZARA should be withheld in patients who develop a serious infection until the infection is controlled. Initiating treatment with KEVZARA is not recommended in patients with a low neutrophil count, ie, absolute neutrophil count (ANC) less than $2 \times 10^3/L$ and in patients with a platelet count below $150 \times 10^3/\mu L$. Please see section 4.2 of KEVZARA Summary of Product Characteristics.

† Once removed from the refrigerator, KEVZARA should be administered within 14 days and should not be stored above 25°C.

AVAILABLE IN EVERY-2-WEEK-DOSING WITH 2 DOSAGE STRENGTHS IN 2 DEVICES*

PRE-FILLED 200 mg SYRINGE[†]



PRE-FILLED 200 mg PEN[†]



[†]Syringe and pen not actual size. Syringe and pen both available in 150 mg.

KEVZARA® (sarilumab) - Abbreviated Prescribing Information

(▼) NAME AND PRESENTATION: KEVZARA 150 mg solution for injection in pre-filled syringe, KEVZARA150 mg solution for injection in pre-filled pen, KEVZARA 200 mg solution for injection in pre-filled syringe, KEVZARA 200 mg solution for injection in pre-filled pen, 150 mg solution for injection: each single-dose pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml). Each single-dose pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml). 200 mg solution for injection: each single-dose pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml). Each single-dose pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml). Sarilumab is a human monoclonal antibody selective for the interleukin-6 (IL-6) receptor, produced in Chinese Hamster Ovary cells by recombinant DNA technology. **THERAPEUTIC INDICATIONS:** KEVZARA is an interleukin-6 (IL-6) receptor antagonist. KEVZARA in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). KEVZARA can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. **POSLOGY AND METHOD OF ADMINISTRATION:** Treatment should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with KEVZARA should be given the patient alert card. **Posology:** the recommended dose of KEVZARA is 200 mg once every 2 weeks administered as a subcutaneous injection. Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations. For important information on dose modification, please refer to the full SmPC. **Special populations:** The safety and efficacy of KEVZARA have not been studied in patients with hepatic impairment, including patients with positive hepatitis B virus (HBV) or hepatitis C virus (HCV) serology. The safety and efficacy of KEVZARA in children up to 18 years of age have not been established. No data are available. No dose adjustment is needed for elderly patients or patients with mild or moderate renal impairment. **Method of administration:** Subcutaneous use. Injection sites (abdomen, thigh and upper arm) should be rotated with each injection.

KEVZARA should not be injected into skin that is tender, damaged, or has bruises or scars. A patient may self-inject KEVZARA or the patient's caregiver may administer KEVZARA if their healthcare professional determines that it is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of KEVZARA prior to use. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients listed in the full SmPC. Active, severe infections. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Patients should be closely monitored for the development of signs and symptoms of infection during treatment with KEVZARA. Treatment with KEVZARA should be withheld if a patient develops a serious infection or an opportunistic infection. A patient who develops an infection during treatment with KEVZARA should also undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including KEVZARA for RA. Treatment with KEVZARA was associated with a higher incidence of decrease in ANC, a reduction in platelet counts, a higher incidence of transaminase elevations, increases in lipid parameters. Use KEVZARA with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with new onset abdominal symptoms such as persistent pain with fever should be evaluated promptly. If anaphylaxis or other hypersensitivity reaction occurs, administration of KEVZARA should be stopped immediately. KEVZARA should not be administered to patients with known hypersensitivity to sarilumab. Avoid concurrent use of live vaccines as well as live attenuated vaccines during treatment with KEVZARA as clinical safety has not been established. RA patients have an increased risk for cardiovascular disorders and risk factors (eg, hypertension, hyperlipidaemia) should be managed as part of usual standard of care. For further details on special warnings and precautions for use see full SmPC. **DRUG INTERACTIONS:** Upon initiation or substitution of KEVZARA in patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, theophylline)

should be performed and the individual dose of the medicinal product should be adjusted as needed. Caution should be exercised in patients who start KEVZARA treatment while on therapy with CYP3A4 substrates (eg, oral contraceptives or statins), as KEVZARA may reverse the inhibitory effect of IL-6 and restore CYP3A4 activity, leading to decreased exposure and activity of CYP3A4 substrate. For further details see full SmPC. **PREGNANCY AND LACTATION:** Women of childbearing potential should use effective contraception during and up to 3 months after treatment. KEVZARA should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab. Because IgG1 are excreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **EFFECTS ON ABILITY TO DRIVE:** KEVZARA has no or negligible influence on the ability to drive or operate machinery. **UNDESIRABLE EFFECTS:** Very common: neutropenia. Common: upper respiratory tract infection, urinary tract infection, nasopharyngitis, oral herpes, thrombocytopenia, hypercholesterolemia, hypertriglyceridemia, transaminases increased, injection site erythema, injection site pruritus. The most common serious adverse reactions were infections. For further details on adverse events see full SmPC. **OVERDOSE:** There is no specific treatment for KEVZARA overdose. In the event of an overdose, the patient should be closely monitored, treated symptomatically, and supportive measures instituted as required. **SPECIAL PRECAUTIONS FOR STORAGE:** Store in a refrigerator (2°C to 8°C). do not freeze. Once removed from the refrigerator, KEVZARA should be administered within 14 days and should not be stored above 25°C. Store pre-filled syringe/pre-filled pen in the original carton in order to protect from light. **PHARMACOLOGICAL PROPERTIES:** Pharmacotherapeutic group: immunosuppressants, interleukin inhibitors; ATC code: L04AC14. **MARKETING AUTHORISATION HOLDER:** sanofi-aventis groupe, 54, rue La Boétie, 75008 Paris, France. **LEGAL CATEGORY:** Medicinal product subject to medical prescription. **DATE LAST REVISED:** June 2017

Abbreviated Prescribing Information based on the EU SmPC as of June 2017.

Before prescribing always refer to your full local prescribing information as this information may vary from country to country.

Reference: 1. KEVZARA Summary of Product Characteristics. Sanofi Aventis, France, August 2017.
2. Genovese MC et al. Arthritis Rheumatol. 2015;67(6):1424-1437.

Building on our successes: The EULAR Strategy 2018–2023

BY SARA FREEMAN

Every 5 years EULAR revisits and updates its overall strategy – this year sees the launch of the 2018–2023 Strategy. Six areas have been identified for particular focus: quality of care, education, the annual congress, research, advocacy, and the internal organisation of EULAR. At the Congress' Opening Plenary Session, EULAR president Prof. Johannes W.J. Bijlsma took the audience through each of these areas to explain EULAR's plans for the next 5 years.

Quality of care

"Up until now, EULAR has formulated extensive recommendations concerning the diagnosis and management of patients with different rheumatic diseases," Prof. Bijlsma said in an interview in advance of his talk. "While we concluded that these are very effective, the recommendations are still not being implemented everywhere."

One of the main quality of care objectives thus is to try to provide more of a package that will enable greater uptake of the advice being given, said Prof. Bijlsma, professor of rheumatology at University Medical Center Utrecht (Netherlands). As such, EULAR would not only make evidence-based recommendations but also provide proposals as to how they can be implemented in daily practice, as well as provide insight on the outcomes that should be measured.

Essentially, EULAR's focus has moved from providing advice that might enact change to care to more of a focus on how best to implement the best practices and treatments to actually deliver real change, Prof. Bijlsma explained.

The overall goal is that by 2023, EULAR will deliver preeminent comprehensive quality-of-care

frameworks for the management of rheumatic and musculoskeletal diseases (RMDs).

Education

EULAR has a long history of providing high-quality educational information and facilitating educational activities for physicians, health professionals in rheumatology, and people with rheumatic and musculoskeletal diseases, Prof. Bijlsma observed.

"We have been quite active in the field of education; the EULAR School of Rheumatology (ESOR) was launched at the Congress last year and continues to be developed," he said. Already, more than 5,000 participants are enrolled in the online courses that ESOR provides, and many other individuals from all over the world participate in the numerous other educational offerings and activities of ESOR.

"What we are aiming for is being the No. 1 provider of education in the field of rheumatic and musculoskeletal diseases by 2023," he said. This already is being achieved via the many online and physical courses that EULAR offers and the various textbooks and journals that EULAR publishes.

The EULAR Congress

The annual EULAR Congress is the premier European event in the scientific calendar for rheumatologists, allied health professionals, and patients. Over the next 5 years, part of the strategy for the Congress is to be more innovative in the way that information is presented and in the way ideas are exchanged. This means moving away from very large lectures toward having more intimate and more interactive sessions.

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Prof. Iain McInnes



Prof. Johannes W.J. Bijlsma



Dieter Wiek

PHOTOS: GIANLUCA COLLA

“We are also looking at making some of our materials accessible via social media,” Prof. Bijlsma said. Other platforms are also being investigated such that “people may not only physically attend the conference but also attend from a distance by digital content.”

Overall, Prof. Bijlsma said that by 2023, EULAR aims to “provide the foremost RMD congress experience, building on the heritage of our outstanding annual meetings.”

Research

As part of the 2012-2017 Strategy, EULAR proposed the creation of a new foundation; that has been achieved with the formation of FOREUM, the Foundation for Research in Rheumatology. The foundation’s mission is to promote research in RMDs as an independent research funding body. EULAR will continue to support FOREUM, which is a not-for-profit organisation based in Switzerland, as part of the 2018-2023 Strategy, EULAR President-Elect Prof. Iain McInnes said at the Opening Plenary Session.

“Our aim is to build on the suite of strategic initiatives that EULAR has put in place to support research here in Europe and with global perspective,” Prof. McInnes said.

The EULAR 2018-2023 Strategy also will use the RheumaMap to help determine what future research needs to be done. This was launched in May last year at the European Parliament in Brussels. It is a “living document that sets out

In regard to EULAR’s advocacy actions, the focus in coming years will be to keep more people with RMDs at work by 2023. “What we’d like to focus on is work, because work is an essential topic. Work means self-esteem. It means not only money; it means satisfaction as well.”

the current unmet needs of people with RMDs and it sets the aims and objectives that we should be seeking to achieve to improve care,” Prof. McInnes said.

Part of the updated EULAR strategy is to create a virtual research centre or platform for RMDs to give researchers who want to work together the opportunity to do so.

“EULAR is not able to fund the research itself, but EULAR is able to stimulate the preparatory work to bring people together and catalyse the brightest minds to focus on the major challenges of our discipline,” Prof. Bijlsma explained.

Advocacy

With regards to advocacy, EULAR has been active at both the European Union and national level, promoting RMDs and thereby placing them on the public and political

agenda. The World Health Organisation, for example, now includes RMDs as a relevant topic.

The focus in the coming years will be to look more specifically at the effect on people’s working lives with the aim of keeping more people with RMDs at work by 2023.

“What we’d like to focus on is work, because work is an essential topic,” Dieter Wiek, EULAR Vice President representing national PARE organisations, said at the Opening Plenary Session. “Work means self-esteem. It means not only money; it means satisfaction as well.

“We’d like to focus on work and what it means, not only for the individual but also what it means for society because we are all taxpayers.”

Organisation of EULAR

As for how EULAR is organised, the goal has changed from leaning toward being a relatively small organisation to one that has more people employed locally to help achieve the strategic goals without undue reliance on external resources.

“We still have the same mission,” Prof. Bijlsma said. That is to reduce the burden of rheumatic diseases on the individual and society and to improve the treatment, prevention, and rehabilitation of musculoskeletal diseases.

“We can only reach our goal if everyone feels part of the organisation and people from all different groups – physicians, health professionals, scientists, and patients – are working together,” Prof. Bijlsma concluded. □

Roche-sponsored satellite symposium at EULAR 2018

The Journey from Clinical Trials to Improving Patient Care

Held on Thursday 14 June 2018

Considerable advances have been made possible in rheumatology through data from randomised controlled clinical trials (RCTs). Supplementing this with real-world evidence (RWE) from different populations can provide additional confidence when treating patients in real-life settings. Physicians are increasingly looking to RWE to provide new insights into diverse aspects of rheumatology and help drive improvements in patient care.



RWE complements the data from RCTs to enhance our understanding and care of patients in daily clinical practice
Prof Ernest Choy, UK

What is real-world evidence (RWE)?

RWE defined as data that are collected outside the constraints of conventional randomised clinical trials (RCTs)

RCT ~ “homogeneous”

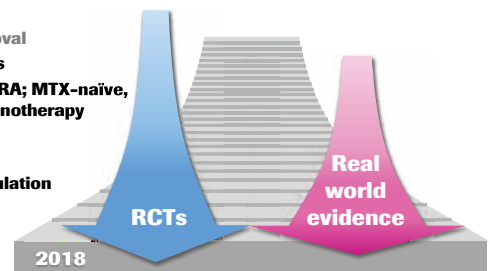


RWE ~ “heterogeneous”



Extensive data generated for TCZ from RCT to RWE across diseases and lifespan

2009 TCZ first approval
Rheumatoid Arthritis
 Moderate to severe RA; MTX-naïve, DMARD/TNF-IR, Monotherapy
Systemic JIA
 Polyarticular JIA
 Subcutaneous formulation
 Early RA
 Giant Cell Arteritis



1 million patients treated with TCZ¹

TCZ=tocilizumab

1. Tocilizumab Periodic Benefit-Risk Evaluation Report (PBRER)

EMA. EuropaBio Info Day (22 November 2016). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500217732.pdf



The elderly patient population

RWE can help physicians make decisions on the best care for their elderly patients
Prof Deborah Symmons, UK



The paediatric patient population

RWE suggests a window of opportunity to treat all forms of juvenile idiopathic arthritis earlier with approved biologics
Prof Fabrizio De Benedetti, Italy



Patients receiving glucocorticoids

RWE informs the optimal use of glucocorticoids in clinical practice to improve patient care
Prof Frank Buttgereit, Germany

EULAR's School of Rheumatology aiming for top provider status by 2023

BY NICOLA GARRETT

EULAR's School of Rheumatology is well on its way to meeting its core objective of becoming the world's leading provider of education in rheumatic and musculoskeletal diseases by 2023.

The EULAR School of Rheumatology (ESOR) was launched at the EULAR Congress in Madrid last year to reflect the changing educational and professional needs of the international rheumatology community.

According to past chair of the EULAR Standing Committee on Education and Training and current EULAR Treasurer, Prof. Annamaria Iagnocco, EULAR has traditionally been a strong supplier of education in rheumatology.

"With the EULAR School of Rheumatology, it has now become the preeminent provider and facilitator of high-quality educational offerings for physicians, health professionals in rheumatology, and people with rheumatic and musculoskeletal diseases worldwide," she said in an interview.

Prof. Iagnocco discussed the current status of the School in a EULAR Projects in Education and Training session.

She explained that, in today's digital era, education opportunities are undergoing constant changes with new approaches, products, and technologies. ESOR is able to match these challenges by offering the rheumatology community a unique model that's easily accessible and meets edu-



Prof. Annamaria Iagnocco

cational needs regardless of geographic location.

"The EULAR School of Rheumatology represents an innovative educational model and reflects the changing needs of the learners through offering new materials as well as facilitating the access to the highest quality of education in the field," she said.

An example of just how the EULAR School of Rheumatology is meeting educational needs through new materials is the launch of a new learning management system – a new-look website and an easy-to-use app.

"The app is very interesting as it contains a lot of material that is very useful ... it allows the rheumatology community to quickly and easily access clinical resources like EULAR Recommendations, classification criteria, and the outcome

measures and imaging libraries," she said.

In addition, Prof. Iagnocco said that in September 2018, there will be a new course on imaging available.

The purpose of this 12-module course is to educate both rheumatologists and future rheumatologists on how to interpret imaging examinations such as conventional radiographs, CT, and MRI in musculoskeletal diseases.

For a membership fee of 30 euros per year, ESOR can access the above mentioned updated EULAR app (including a Spanish version of the pocket primer), receive information on new courses, have access to discounts, print their course completion certificates, and gain easy access to the details of the curriculum they've just studied.

"All EULAR activities are very prestigious and can be a useful way for young rheumatologists to showcase the education and the courses they have completed in the field of rheumatology," Prof. Iagnocco noted.

One thing is for certain, she said: The future of the ESOR looks very promising.

"A team of experts already is working to develop even more new projects addressed to all EULAR pillars, the number of attendees to EULAR educational activities is constantly increasing, and with the new platform, we expect additional access from different areas of the globe." □

'Don't Delay, Connect Today' campaign begins its second year

BY IAN LACY

EULAR's "Don't Delay, Connect Today" campaign is now in its second year after launching at the EULAR 2017 Congress in Madrid, and speakers this year in Amsterdam geared up again to promote the campaign and describe its implementation so far. At a PARE session, Prof. Gerd R. Burmester, Prof. Tanja A. Stamm, Prof. Ruxandra Ionescu, and several other speakers addressed different facets of the campaign.

Why we need the 'Don't Delay, Connect Today' campaign

Prof. Burmester, Past President of EULAR and professor of medicine at Berlin's Charité University Clinic, spoke about the importance of the campaign, which "aims to raise awareness of the early diagnosis in preventing further damage for people with rheumatic and musculoskeletal diseases (RMDs) and to encourage timely access to evidence-based treatment."

Early diagnosis of RMDs is particularly important because most people receive a delayed diagnosis or no diagnosis at all, according to Prof. Burmester.

"Awareness of the importance of early diagnosis is limited amongst the general public, people with RMDs, and many doctors and health professionals in rheumatology (HPRs). For example, fibromyalgia remains undiagnosed in as many as three out of four people with the condition, and diagnosis time averages 5 years."

The EULAR campaign also is encouraging patients to see physicians soon after symptoms appear.

"EULAR hopes to encourage people to connect with their doctor when possible RMD symptoms appear, such as persistent joint and muscle pain, extreme fatigue, and

stiffness. "Don't Delay, Connect Today" also aims to help doctors and HPRs identify and treat diseases as early and accurately as possible."

By encouraging people to work together, positive steps can be taken to improve the lives of those living with RMDs, according to Prof. Burmester.

"By uniting everyone connected to the RMD community through "Don't Delay, Connect Today," we can work together to create significant positive change for people with RMDs. We want to ensure EULAR continues to place early diagnosis, access to treatment, and the needs of RMD patients at the heart of everything we do."

How HPRs can support the campaign

HPRs can play a critical role in the early treatment of inflammatory conditions, according to Prof. Stamm of the Medical University of Vienna.

"HPRs refer patients early to medical specialists, if needed. Nurses, physiotherapists, and occupational therapists can identify patients with inflammatory conditions and refer them to rheumatologists early for timely and evidence-based care."

In fact, "physiotherapists can distinguish patients with early inflammatory arthritis from those without," with 89% concordance with a rheumatologists' subsequent diagnosis, she said. Occupational therapists also can decide whether patients require hospital admission or not in emergency care settings.

HPRs also play an important role in osteoarthritis care, according to Prof. Stamm, who is EULAR Vice President representing HPRs.

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Prof. Tanja A. Stamm



Prof. Gerd R. Burmester



Prof. Ruxandra Ionescu

PHOTOS: GIANLUCA COLLA

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“HPRs provide timely, evidence-based care for osteoarthritis [that] reduces symptoms, comorbidity risk, and need for expensive surgical procedures.”

Timely intervention with osteoarthritis is important because of the lack of medical drug treatments. Apart from drug interventions, one of the best ways to combat osteoarthritis is through healthy living and prevention both at home and in the workplace, she said.

“Occupational therapists, physiotherapists, and nurses apply ergonomic principles to make the work setting as healthy as possible and prevent RMDs and further comorbidities.”

Implementation of the EULAR campaign in Romania

The “Don’t Delay, Connect Today”

campaign has been an important initiative in Romania, according to Prof. Ionescu, president of the Romanian Society of Rheumatology and General Secretary of EULAR.

“More than 600,000 people in Romania (3% of the total population), out of which 2,000 are children, suffer from inflammatory rheumatic diseases that are included in the RMDs category,” she said.

The aim of the campaign in Romania has been similar to the aim of the campaign overall – to increase awareness of rheumatic diseases and encourage people to seek medical attention. Raising awareness includes providing information on signs and symptoms that may prompt individuals to seek a rheumatologist’s advice.

The campaign is not only attempting to reach Romanian cit-

izens but also those deciding on policy. Prof. Ionescu stated that individuals in the Health Ministry, Insurance House, and Parliament must be aware of the effects that rheumatic diseases can have on the population and the need to supply funding for medical care.

Prof. Ionescu also discussed some of the major challenges the campaign has faced.

“[Some] major challenges we faced in clinical activity refer to insufficient funds from health care, insufficient number of rheumatologists, reluctance of patients to go early to rheumatologists. In most cases, the rheumatologist usually first sees the patient after he already has disabilities as a result of RMDs, making remission impossible, as the evolution of destructive lesions leads to an irreversible functional deficit.”



EULAR School of Rheumatology

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#ESOR



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eular
fighting rheumatic & musculoskeletal diseases together

The future of rheumatology care will need to be team based

BY GREGORY TWACHTMAN



Dr. Yvonne van Eijk-Hustings



Barbara Slusher



Dr. Hubertus J.M. Vrijhoef

As rheumatologists are faced with greater demands on their time that take away from the patient experience, such as quality measurement programmes and regulations surrounding electronic health records, it is going to take a wider range of medical professions to maximise time and guarantee the delivery of quality care.

Utilisation of medical professionals to complement the work of the physician was the subject of a session on “Sustainable Healthcare in Rheumatology and the Role of Health Professionals.”

“The same model of health care from the 1950s, ‘60s, ‘70s, ‘80s, and ‘90s is no longer sustainable,” Barbara Slusher, assistant professor of instruction in the department of physician assistant studies at the University of Texas Medical Branch at Galveston, USA, said. “We have to look at different models of how to deliver care.”

She noted that there are a multitude of health care professionals now with doctorate-level degrees who provide support services to physicians, and they need to be

used more often in the delivery of care.

“There are significant data to show that we will not have enough rheumatologists to provide care to the ageing population,” Ms. Slusher said.

She said that increasing the number of fellowship positions for advanced training for physicians as well as adding even more physician assistants and nurse practitioners is not going to meet the needs.

“We need to look for another solution to the healthcare problem of not having enough providers,” she continued. She presented the current scenario in medicine – increased burnout, decreased well-being in the physician population, increased workload demands based on electronic health records, government requirements for measuring what we do, decreased reimbursement for the services – and then presented a model of team-based care that looks at utilising other health professions within rheumatology practices to be an answer to the capacity demand issue.

She said that rheumatologists can

borrow from primary care to build what is called “teamlets” that expand the roles of medical assistants to do a more extensive previsit with patients and taking vitals, they could also help to document and chart information. The medical assistant could also do the postvisit to make sure the patient understands the outcome of the visit.

“If they understand the nature of their disease, they are much more adherent to the plan that we make” to treat their condition, she said. A teamlet model could help improve patient outcomes and satisfaction as well as provider satisfaction and help reduce burnout.

She also suggested more leveraging of pharmacists when it comes to managing medications, as well as using social workers to help improve patient engagement and to help the physician answer questions about quality-of-life issues and other concerns related to managing their disease.

Yvonne van Eijk-Hustings, PhD, senior researcher and rheumatol-

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ogy nurse at Maastricht (Netherlands) University Medical Centre, focused specifically on the role of the nurse in the delivery of care, including reviewing the update of the EULAR recommendations of the role of the nurse. She gave her presentation in the context of the triple aim of improving health outcomes, improving the patient experience, and reducing costs.

“Nurses can be involved in all different parts of the [healthcare] process,” said Dr. van Eijk-Hustings, who presented information from different nations on how they use nurses within the delivery of care.

Reaching the point of a greater role could be a challenge in some systems, such as those in which nurses may not be as valued or in those with differing parameters for reimbursement. In other healthcare

systems, nurses already are a key part of the delivery and not much culture change would be required to potentially expand that role.

“Sustainable healthcare is often associated with low-cost health care, and I really hope that people will see that it’s not only because nurses are cheap that they contribute to sustainable healthcare, but they also add something,” she said.

Hubertus J.M. Vrijhoef, PhD, CEO of Panaxea of Amsterdam, discussed integrated care models and looked at some of the needs that exist in order to understand how well these models of delivery work.

“There is a lack of overview on integrated models of care, as well as the need for their evaluation, evidence-based guidelines, and organisational recommendations,” he said.

“By mapping models according to

the WHO Framework on integrated people-centred health services and IHI’s [Institute for Healthcare Improvement’s] Triple Aim dimensions, we provide a systematic approach for understanding and comparing new integrated care models. This may benefit those preparing themselves for and those involved in redesigning their practice.”

His talk came from a literature review of 63 articles that examined 53 integrated delivery models across 16 nations.

“The literature reveals heterogeneity in models when looking at their goals, strategies applied, and improvement dimensions reported,” he said. “When no ‘one size fits all’ approach towards new integrated care models exists, it becomes important to know ‘one’s size’ when adopting, adapting, or comparing oneself with other models.” □



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New classification criteria reset SLE definition

BY MITCHEL L. ZOLER

The new systemic lupus erythematosus classification criteria of EULAR and the American College of Rheumatology (ACR) are based on a point system that will produce a “paradigm shift” in how the disease gets studied going forward, said Dr. Sindhu Johnson while presenting the latest version of the newly revised classification scheme at the Congress.

Until now, classification of systemic lupus erythematosus (SLE) was a yes-or-no decision, based on whether the patient had a minimum number of characteristic signs or symptoms. The new criteria, which are on track for formal endorsement by EULAR and ACR before the end of 2018, instead use a point system that gives varying weight to each of the 22 criteria. A patient needs to

score at least 10 points from these criteria, and all patients classified with SLE also must have an antinuclear antibody (ANA) titer of at least 1:80 on HEp-2 cells or an equivalent positive test. This means that the criteria also can define patients who just miss classification with SLE by meeting the ANA standard and by tallying 8 or 9 points, and the criteria also identify patients who far exceed the classification threshold by having the requisite ANA plus racking up as many as, perhaps, 20 or 30 points.

New ACR and EULAR criteria for classification of SLE

All patients classified as having systemic lupus erythematosus must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2-positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts:

Clinical domains	Points	Immunologic domains	Points
Constitutional domain		Antiphospholipid antibody domain	
Fever	2	Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Cutaneous domain		Complement proteins domain	
Nonscarring alopecia	2	Low C3 or low C4	3
Oral ulcers	2	Low C3 and low C4	4
Subacute cutaneous or discoid lupus	4	Highly specific antibodies domain	
Acute cutaneous lupus	6	Anti-dsDNA antibody	6
Arthritis domain		Anti-Smith antibody	6
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6		
Neurologic domain			
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis domain			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Hematologic domain			
Leukopenia	3		
Thrombocytopenia	4		
Autoimmune hemolysis	4		
Renal domain			
Proteinuria >0.5g/24 hr	4		
Class II or V lupus nephritis	8		
Class III or IV lupus nephritis	10		

MDeDge News

“This is a real research opportunity,” to follow patients who fall just short with 8 or 9 points to assess their longer-term prognosis, as well as to study whether “higher scores mean a higher risk for developing a bad outcome,” said Dr. Johnson, a rheumatologist at the University of Toronto and director of the Toronto Scleroderma Program. Other areas for future research with the new criteria include seeing how they work in various SLE subgroups, such as patients with renal-predominant disease or skin-predominant disease, and also seeing how they work in various ethnic populations.

Dr. Johnson acknowledged the importance the new classification criteria will have for diagnosing SLE in routine practice, even though the ACR and EULAR both stress that the classification criteria are intended only for research and not for diagnosis.

“Diagnosis of lupus still falls within the realm of the treating physician,” but the classification criteria “inform our concept of the disease,” Dr. Johnson said in an interview. “The new criteria allow for a shift in the way we think of the disease.”

For example, for the first time, the new criteria include fever as a classification criterion, which receives 2 points if an infectious or other

MDeDge News

Source: Dr. Johnson

continued on following page



ROBERT LODGE/MD EDGE NEWS

VIDEO HIGHLIGHTS: [Click here](#) to watch a video interview with Prof. Thomas Dörner, professor of medicine at Charité–Universitätsmedizin Berlin and codeveloper of the guidelines.

SLE classification criteria perform well in validation study

BY SARA FREEMAN

The first EULAR and American College of Rheumatology joint criteria for classifying systemic lupus ery-

thematosus have a sensitivity and a specificity of more than 90%.

This is important because they improve upon the existing ACR and Systemic Lupus International

Collaborating Clinics (SLICC) criteria, said Prof. Martin Aringer, who cochaired the Steering Committee that produced the new classifica-

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non-SLE cause can be discounted. Fever has recently been identified as a marker of early-stage SLE in at least some patients, and its addition to the classification criteria “adds a new dimension to how we think about the disease and allows us to distinguish early disease from mimicking diseases,” she explained. At the other end of the classification spectrum, a finding of class III or IV lupus nephritis on renal biopsy receives 10 points, and hence, this one finding plus having a high enough level of ANA leads to SLE classification regardless of whether the patient has any other signs or symptoms of the disease.

That’s because “85% of our ex-

perts said that they would feel confident classifying a patient as having lupus based only on a renal biopsy” and ANA positivity, said Dr. Johnson, who served as the ACR-appointed cochair of the criteria-writing panel along with a cochair selected by EULAR, Prof. Martin Aringer, professor of medicine and chief of the division of rheumatology at the Technical University of Dresden (Germany). She cautioned that other levels of lupus nephritis, class II or V, confer only 8 points to the classification and so by themselves are not enough to label a person as having lupus.

During her presentation, Dr. Johnson cited the high levels of sensitivity and specificity that the new

classification criteria demonstrated in a validation cohort of more than 1,000 cases and controls. In the validation analysis, the new criteria had a sensitivity of 96.12% and specificity of 94.43% for classifying SLE, giving the new criteria a better result on both these measures than either the 1997 ACR criteria (Arthritis Rheum. 1997 Sept;40[9]:1725) or the 2012 Systemic Lupus International Collaborating Clinics criteria (Arthritis Rheum. 2012 Aug;64[8]:2677-86).

The 22 criteria cluster into seven separate clinical domains and three different immunologic domains (see chart). The point values assigned to each criterion range from 2 to 10 points.

Dr. Johnson had no disclosures. □

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tion criteria and is professor of medicine and chief of the division of rheumatology at the Technical University of Dresden (Germany).

Most clinicians working with lupus are familiar with the 1997 ACR criteria for the classification of sys-

“We had the feeling, and this is now confirmed by the new classification criteria, that a number of patients studied in earlier trials may not have fulfilled what we think is the classical lupus profile, so-called lupus or SLE mimickers.”

temic lupus erythematosus (SLE), which “had a relatively simple structure,” Prof. Aringer said during the opening plenary abstract session at the Congress. These considered items such as the presence of malar or discoid rash, photosensitivity, oral ulcers and arthritis, among others. These had a high specificity but a lower sensitivity. The development of the SLICC criteria in 2012 improved upon the sensitivity of the ACR criteria (92%-99% vs. 77%-91%), but at a loss in specificity (74%-88% vs. 91%-96%).

The SLICC criteria introduced two novel ideas, said Prof. Aringer. The first was that there had to be at least one immunologic criterion met, and the second was that biopsy-proven lupus nephritis had to be present with antinuclear antibodies (ANA) and anti-DNA antibodies detected.

One of the goals in developing the joint EULAR/ACR criteria therefore was to try to maintain the respective sensitivity and specificity achieved with the SLICC and ACR criteria. One of the key things that

the new criteria looked at was to see if ANA could be used as an entry criterion. Investigations involving more than 13,000 patients with SLE showed that it could, with a antibody titer threshold of 1:80, exhibit a sensitivity of 98% (Arthritis Care Res. 2018;70[3]:428-38). Another goal was to see if histology-proven nephritis was a stronger predictor of SLE than clinical factors, such as oral ulcers, and to identify items that would only be included if there was no other more likely explanation (Lupus. 2016;25[8]:805-11).

Draft SLE classification criteria were developed based on an expert Delphi process and included ANA as an entry criterion and items weighted according to the likelihood of being associated with lupus. Items considered included the presence and severity of lupus nephritis, serology and other antibody tests, skin and central nervous system involvement, and haematologic and immunologic criteria such as the presence of thrombocytopenia and low complement (C3 and/or C4).

Prof. Aringer described how these criteria had been derived and now validated in a large international cohort of individuals with and without SLE. In total, 23 expert centres participated in this process, each contributing up to 100 patients each with SLE or non-SLE diagnoses. Three independent reviewers confirmed each patient’s diagnosis, with 1,160 patients with SLE and 1,058 without SLE finally identified. Of these, 501 and 500 were randomly allocated to a derivation cohort and 696 and 574 to a validation cohort.

“Performance characteristics find sensitivity similar to the SLICC criteria while maintaining the specificity of the ACR 1997 criteria,” Prof. Aringer said.

The sensitivity and specificity of the new criteria were 98% and 96% in the derivation cohort and 96% and 93% in the validation cohort.

“I was really very pleased and

very happy to see that the revised or the new ACR/EULAR classification criteria had sensitivity and specificity of above 90%,” Prof. Thomas Dörner, said in an interview at the Congress. Prof. Dörner was a codeveloper of these criteria.

Over the past 10-15 years there have been several therapies that have failed to live up to their early promise as a potential treatment for lupus, said Prof. Dörner, professor of medicine at Charité-Universitätsmedizin Berlin. He noted that the failed treatment trials had led investigators to try to determine ways in which lupus might be best treated, such as by a “treat-to-target” approach to attain remission and low disease activity. It also led to the reevaluation of how lupus is classified to see if that might be affecting the population of patients recruited into clinical trials.

“We had the feeling, and this is now confirmed by the new classification criteria, that a number of patients studied in earlier trials may have not fulfilled what we think is the classical lupus profile, so-called lupus or SLE mimickers,” Prof. Dörner said. This could have affected the chances of a treatment approach being successful versus placebo.

The new classification criteria are similar to those in other rheumatic diseases in that they give different weight to the effects on different organ systems, Prof. Dörner said. The stipulation that there must be a positive ANA test is also an important step, “really to make sure that we are looking at an autoimmune disease and nothing else,” he observed.

For patients who do not have a positive ANA test, they can of course still be treated, Prof. Dörner reassured, but for the classification criteria and entering patients into clinical trials, it’s really important to have strict classification criteria so that the results may be compared.

Prof. Aringer and Prof. Dörner had no relevant disclosures besides their involvement in developing the new classification criteria. □

LLDAS shows potential as routine lupus treatment target

BY MITCHEL L. ZOLER

The Lupus Low Disease Activity State measure of treatment response offers clinicians an attainable target for patients with systemic lupus erythematosus that correlates with a substantially reduced rate of organ damage, based on a retrospective assessment of data collected from more than 2,000 lupus patients at a single U.S. centre.



Dr. Michelle A. Petri

The analysis showed that when patients with systemic lupus erythematosus (SLE) met the Lupus Low Disease Activity State (LLDAS) criteria at least half the time while on treatment, their overall rate of organ damage was reduced by 52%, compared with patients who never achieved LLDAS, Dr. Michelle A. Petri said at the Congress.

Fulfilling the LLDAS criteria more than half the time "is an easier goal to achieve" than other measures of SLE activity, and "more realistic" as a treatment target for both clinical trials as well as in routine practice, said Dr. Petri, pro-

fessor of medicine and director of the Lupus Center at Johns Hopkins University, Baltimore.

"LLDAS is something that anyone can use in practice," and has the advantage of including a low glucocorticoid dose – no more than 7.5 mg prednisolone/day or an equivalent glucocorticoid – as one of its criteria, "a major bad actor" for SLE patients, Dr. Petri said in an interview. LLDAS "is absolutely ready for routine use," although until now few clinicians have used it to monitor SLE patients, she noted.

"The LLDAS can be a useful target," commented Prof. Ian N. Bruce, professor of rheumatology at the University of Manchester (England), adding that the glucocorticoid dosage an SLE patient receives "is an important parameter to measure when assessing an SLE patient.

"It's not far from being ready for routine use, but I'd like to see more evidence" that it's a meaningful measure of an SLE patient's disease status, he said in an interview.

To examine the clinical relevance of the LLDAS criteria, a five-point assessment for SLE first introduced in a 2016 report (*Ann Rheum Dis.* 2016 Sept;75[9]:1615-21), Dr. Petri and her associates applied it retrospectively to their records for 2,026 SLE patients in a Johns Hopkins registry. Clinicians at Johns Hopkins routinely assessed their SLE patients every 3 months and followed the patients for a median of about 10 years, and so had data from more than 81,000 patient encounters. The researchers used the longitudinal follow-up records to calculate an area under the curve for each patient that tracked their LLDAS state over time. This showed a clear dose-response relationship: The

more time an SLE patient spent in LLDAS, the less organ damage they had. Patients who remained in LLDAS at least 75% of the time had a 60% reduction in cumulative organ damage, compared with patients who never achieved LLDAS, Dr. Petri said. The analysis also showed that LLDAS was substantially easier for patients to achieve than the Definitions of Remission in SLE (*Ann Rheum Dis.* 2017 March;76[3]:554-61). The Johns Hopkins cohort met the LLDAS definition about three times more often than they met the Definitions of Remission in SLE criteria, Dr. Petri said.

The new analysis also showed that LLDAS was especially effective in correlating with statistically significant reductions in future strokes, MI, and end-stage renal disease, though it did not significantly correlate with subsequent reductions in the incidence of cognitive impairment, deep vein thrombosis, malignancy, pulmonary fibrosis, pulmonary hypertension, or cataract development. But the strong correlation of time in LLDAS and the future rate of stroke, MI, or end-stage renal disease was very meaningful because those are the most important types of damage associated with SLE, Dr. Petri said. "LLDAS is a good treatment target as a surrogate" for future risk of SLE complications.

The study had no commercial funding, and Dr. Petri had no disclosures to report. Dr. Bruce has been a consultant to and speaker for GlaxoSmithKline, MedImmune, Pfizer, Roche, and UCB, and he has received research support from Genzyme, GlaxoSmithKline, Human Genome Sciences, Roche, and UCB. □

EULAR nears first recommendations for managing Sjögren's syndrome

BY MITCHEL L. ZOLER

The first recommendations from a rheumatology society for managing patients with Sjögren's syndrome are nearing finalisation by a EULAR task force, and they divide the treatment targets into sicca syndrome and systemic manifestations of the disease.



Prof. Soledad Retamozo

"In Sjögren's, we always have two subtypes of patients: those who have sicca syndrome only, and those with sicca syndrome plus systemic disease," explained Prof. Soledad Retamozo, who presented the current version of the recommendations at the Congress. "We wanted to highlight that there are two types of patients," said Prof. Retamozo, a rheumatologist at the University of Córdoba (Argentina). "It's hard to treat patients with sicca syndrome plus fatigue and pain because there is no high-level evidence on how to do this; all we have is expert opinion," she said in an interview.

In fact, roughly half of the recommendations have no supporting evidence base, as presented by Prof. Retamozo. That starts with all three general recommendations she presented:

- Patients with Sjögren's should be managed at a centre of expertise using a multidisciplinary approach, which she said should include ophthalmologists and

dentists to help address the mouth and ocular manifestations of sicca syndrome.

- Patients with sicca syndrome should receive symptomatic relief with topical treatments.
- Systemic treatments – glucocorticoids, immunosuppressants, and biologicals – can be considered for patients with active systemic disease.

The statement's specific recommendations start with managing oral dryness, beginning with measuring salivary gland (SG) dysfunction. The document next recommends nonpharmacologic interventions for mild SG dysfunction, pharmacological stimulation for moderate SG dysfunction, and a saliva substitute for severe SG dysfunction. All three recommendations are evidence based, relying on results from either randomised trials or controlled studies.

The second target for topical treatments is ocular dryness, which starts with artificial tears, or ocular gels or ointments, recommendations based on randomised trials. Refractory or severe ocular dryness should receive eye drops that contain a nonsteroidal anti-inflammatory drug or a glucocorticoid, based on controlled study results, or autologous serum eye drops, a strategy tested in a randomised trial.

The recommendations then shift to dealing with systemic manifestations, starting with fatigue and pain, offering the expert recommendation to evaluate the contribution of comorbid diseases and assess their severity with tools such as the EULAR Sjögren's Syndrome Patient-Reported Index (ESSPRI) (Ann Rheum Dis. 2011 Jun;70[6]:968-72), the Profile of Fatigue, and the Brief Pain Inventory.

Using evidence from randomised trials, the recommendations tell

clinicians to consider treatment with analgesics or pain-modifying agents for musculoskeletal pain by weighing the potential benefits and adverse effects from this treatment.

For other forms of systemic disease, the recommendations offer the expert opinion to tailor treatment to the organ-specific severity using the ESSPRI definitions. If using glucocorticoids to treat systemic disease, they should be given at the minimum effective dose and for the shortest period of time needed to control active systemic disease, a recommendation based on retrospective or descriptive studies. Expert opinion called for using immunosuppressive treatments as glucocorticoid-sparing options for systemic disease, and this recommendation adds that no particular immunosuppressive agent stands out as best, compared with all available agents.

Finally, for systemic disease the recommendations cited evidence from controlled studies that B-cell-targeted therapies, such as rituximab and belimumab, may be considered in patients with severe, refractory systemic disease. An additional expert opinion was that the systemic, organ-specific approach should sequence treatments by using glucocorticoids first, followed by immunosuppressants, and finally biological drugs.

The recommendations finish with an entry that treatment of B-cell lymphoma be individualised based on the specific histopathologic subtype involved and the level of disease extension, an approach based on results from retrospective or descriptive studies.

The recommendations must still undergo final EULAR review and endorsement, Prof. Retamozo said.

She had no disclosures. □

ACR and EULAR to review new criteria for classifying vasculitis

BY SARA FREEMAN

New classification criteria for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides have been drafted and now need formal review by the American College of Rheumatology and EULAR before they can be put into practice.

These draft criteria – which are based on data collected via the Diagnostic and Classification Criteria in Vasculitis (DCVAS) observational study – focus on how to classify three main types of ANCA-associated vasculitis: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA).

According to Dr. Joanna Robson, the chair of the DCVAS steering committee, these new criteria better “reflect current practice by incorporating, but not relying on, ANCA testing and advanced imaging.”

There has been a consensus conference held at Chapel Hill (Arthritis Rheum 2013;65[1]:1-11) that identified MPA as a separate entity, and ANCA testing has become routine practice, explained Dr. Robson of the University of the West of England in Bristol. Computed tomography and magnetic resonance imaging are also now used to help differentiate between the different vasculitides.

“This really has been a collaborative, multinational effort,” Dr. Robson said at the Congress. To develop the draft criteria, the steering committee collated data from 135 sites in 32 countries on more than 2,000 patients. These had been collected as part of the ACR/EULAR-run DCVAS study, which has been coordinated at the University of Oxford since 2011.

Three phases were used to develop these criteria: First an expert panel reviewed all cases in the DCVAS to identify those that they felt were attributable to small-vessel vasculitis. Second, variables that

might be appropriate to use in the models were examined, with more than 8,000 individual DCVAS items considered and then whittled down to 91 items and then sifted again to form a clear set of 10 or fewer items. Third, statistical analyses combined with expert review were used to develop the criteria and then validate these.

Dr. Robson reported that of 2,871 cases identified as ANCA-associated vasculitis, 2,072 (72%) were agreed upon by the expert review panel. Of these, there were 724 cases of GPA, 291 of MPA, 226 of EGPA, and around 300 cases of other small-vessel vasculitis or polyarteritis nodosa. To develop the criteria, the GPA cases were used as the “cases” and the other types of vasculitis as the comparators, Dr. Robson explained.

For GPA, MPA, and EGPA, a set of items (10, 6, and 7, respectively) were derived and scored, positively or negatively, and a cutoff determined at which a classification of the particular vasculitis could be made. During discussion, Dr. Robson noted that the threshold score for a classification of EGPA (greater than or equal to 6) had been set slightly higher than for GPA or MPA (both greater than or equal to 5) “because of the clinical problem of there being very close comparators which can actually mimic EGPA.” This is where the negative scoring of some items used in these criteria are very important, she said.

The 10-item GPA criteria included three clinical (such as the presence of bloody nasal discharge upon examination) and seven investigational (such as cytoplasmic ANCA positivity) items. These criteria were found to have a high sensitivity (92%) and specificity (94%) for identifying GPA.

The six-item MPA criteria included one clinical item (bloody nasal

discharge, which was this time attributed a negative score) and five investigational items (with ANCA testing given a higher positive score than for GPA). The sensitivity and specificity of these criteria were a respective 91% and 94%.

Finally, the seven-item EGPA crite-



Dr. Joanna Robson

ria included three clinical items (including obstructive airways disease and nasal polyps) and four investigational items (with ANCA positivity given a negative score). These criteria had an 85% sensitivity and 99% specificity for EGPA.

Dr. Robson emphasised that all these classification criteria were to be used only after exclusion of other possible causes of vasculitis and after a “diagnosis of small- or medium-vessel vasculitis has been made.”

These criteria are to help classify into the subtypes of vasculitis “primarily for the purpose of clinical trials,” she said. “The next steps are review by the EULAR and ACR committee, and only on final approval will these criteria be ready to use.”

DCVAS is sponsored by the University of Oxford (England) with funding from EULAR, ACR, and the Vasculitis Foundation. Dr. Robson had no relevant financial disclosures.

SARA FREEMAN/MEDGEE NEWS



Limited anakinra course often enough for systemic JIA, if used first

BY TED BOSWORTH



Dr. Sebastiaan J. Vastert

Rather than waiting for other drugs or immunotherapies to fail, an immediate up-front but time-limited course of an interleukin-1 receptor (IL-1R) antagonist induced rapid and sustained remissions in most children with systemic juvenile idiopathic arthritis (JIA), according to 5-year data presented at the Congress.

In the latest follow-up of a protocol first described in 2014, over 90% of patients still had inactive disease, 75% of whom were completely off therapy, reported Dr. Sebastiaan J. Vastert of the division of pediatrics at University Medical Centre, Utrecht (Netherlands).

The proportion of sustained responses with a limited course of upfront anti-IL-1R is greater than that reported for this or other biologics when used second line, according to Dr. Vastert. He be-

lieves that the timing of anti-IL-1R treatment is critical to the high response rates seen so far.

“Translating this into clinical practice, you could say that there might be a window of opportunity early in systemic JIA in which the innate immune system is the major player and perhaps you could downregulate this to control the inflammation,” Dr. Vastert explained.

Citing a series of experimental studies at his institution that suggest immune mediators change as systemic JIA evolves from an acute to a chronic phase, Dr. Vastert believes that early use of an anti-IL-1R therapy may alter the trajectory of systemic JIA, compared with when it goes untreated or is treated with conventional therapies.

In the original series reported in 2014 (*Arthritis Rheumatol.* 2014 Apr;66:1034-43), data were presented on 20 patients. All fulfilled the International League of Associations for Rheumatology criteria for systemic JIA. They were treated with anakinra after failing to respond to indomethacin but before receiving any other therapy, including glucocorticoids, disease-modifying antirheumatic drugs, or other biologics.

In the protocol described in the initial publication, a stop-therapy strategy permitted treatment discontinuation after 3 months in those who met American College of Rheumatology criteria for 90% improvement (ACR Pedi 90) in JIA.

By 1 year, 73% of the patients had met criteria to stop therapy. Of 11 patients followed for 3 years, 10 met criteria for disease remission, 8 of whom were off medication. The remaining two continued to receive anti-IL-1R or another therapy.

The systemic JIA cohort at Dr. Vastert’s institution has now grown

to 50 patients, of whom 42 patients have received first-line anakinra. Among the 25 patients who have been followed for at least 5 years, 72% have inactive disease, as defined by ACR Pedi 90 criteria off therapy. Another 20% have inactive disease on therapy, which is anakinra or another biologic in most cases. The majority of patients have avoided glucocorticoids completely.

Freedom from glucocorticoids has been accompanied by high rates of satisfaction and has allowed patients to avoid adverse events associated with glucocorticoids. For example, only one patient in this series has a growth curve more than two standard deviations below normal for age and gender, according to Dr. Vastert.

“This is just a single-centre cohort study, but we now have 3 more years of data to be convinced of this concept,” Dr. Vastert said.

Another notable finding from this cohort: 12 patients have been enrolled who did not fulfill International League of Associations for Rheumatology criteria for systemic JIA because of the absence of joint involvement. Strongly suspected of having systemic JIA because of other clinical signs and features, these patients have also responded well to first-line anakinra therapy.

“Our data point to a classification [of systemic JIA] that does not include arthritis as a prerequisite for diagnosis,” said Dr. Vastert, who provided data suggesting that elevated levels of IL-18 might be among biomarkers that could be employed in a revised classification system.

The study was not funded by industry. Dr. Vastert reported receiving consulting fees from Novartis. □

Glucocorticoid-tapering guidelines described for new-onset juvenile dermatomyositis

By Ted Bosworth

An evidence-based protocol for the tapering and discontinuation of glucocorticoids in children with juvenile dermatomyositis (JDM) provides the first evidence-based strategy for glucocorticoid tapering in this disorder.

“We decided to validate an evidence-based protocol used in the PRiNTO [Paediatric Rheumatology International Trials Organisation] study, which included a large population of new-onset JDM patients for evaluation,” explained Dr. Gabriella Giancane of the Paediatric and Rheumatology Clinic at Istituto Giannina Gaslini, Genoa, Italy.

In the PRiNTO trial, 139 previously untreated children with new-onset JDM were randomised to one of three treatment arms; all children initiated therapy on intravenous methylprednisolone. One group continued on prednisone alone, another received prednisone with ciclosporin, and a third group received prednisone with methotrexate.

The major findings of that trial, which showed the addition of ciclosporin or methotrexate to be more effective than prednisone alone, were published more than 2 years ago (Lancet. 2016;387[10019]:671-8), but Dr. Giancane and her coinvestigators evaluated whether the glucocorticoid-tapering protocol employed in that study can be used in routine patient care.

In PRiNTO, tapering started after the first month, gradually reaching the safe dose of 0.2 mg/kg per day at month 6 from the initial dose of 2 mg/kg per day. In patients who remained in remission, discontinuation of prednisone was allowed at month 24.

In the analysis that Dr. Giancane presented at the Congress, she

evaluated this protocol in order to derive evidence-based recommendations. The secondary objective of the study was to identify predictors of clinical remission and successful glucocorticoid discontinuation.

Patients who achieved clinical remission and discontinued prednisone without any major therapeutic change, defined as the addition or major increase in dose of a disease-modifying agent, served as a reference group. On the basis of core set measures, such as Childhood Myositis Assessment Scale and manual muscle testing, they were compared with two groups of patients who did not achieve clinical remission: those who did not require a subsequent major therapeutic change and those who did.

After 2 months from the start of therapy, the relative changes in disease activity measures in the reference group and the two comparative groups provided the basis of the tapering protocol that Dr. Giancane described.

Overall, the data suggest that improvements in disease activity measures within 6 months are predictive of the ability to achieve glucocorticoid tapering without loss of disease control. In those with the most favourable characteristics, which includes age older than 9 years and rapid reductions in disease activity parameters over the first 2 months, the probability of clinical remission was up to seven times greater than in those with less favourable characteristics.

“The key value of this study is that it is evidence based. The data identify predictors of clinical remission and glucocorticoid discontinuation that allow the clinician to identify JDM patients at a higher



MITCHELL L. ZOLER/MDERGE NEWS

Dr. Gabriella Giancane

risk of a bad outcome very early in the treatment course,” Dr. Giancane said. She suggested this information is useful, not only for guiding therapy, but also for advising patients and parents about disease prognosis.

Overall, these data validate key clinical measures as simple and practical tools for managing JDM, including how and when to taper glucocorticoids. “We strongly recommend the use of core set measures in evaluating and following patients” as well as for glucocorticoid tapering, Dr. Giancane said. “We now use this protocol routinely in patients at our own centre, although deviations are possible according to disease course.”

Dr. Giancane and her colleagues had no disclosures to report. □



VIDEO HIGHLIGHTS: [Click here](#) to watch a video interview with Prof. Frank Buttgereit of the department of rheumatology at Charité–Universitätsmedizin Berlin.

EULAR recommendations on glucocorticoids: ‘As necessary, but as little as possible’

BY SARA FREEMAN

Glucocorticoids remain an important therapeutic option for many patients with rheumatic and non-rheumatic disease, but careful assessment of their relative benefits and risks needs to be made when prescribing, according to an expert summary of currently available EULAR recommendations that was presented at the Congress.

While effective at reducing inflammation and providing immunosuppression, glucocorticoids are, of course, not without their well-known risks. Some of the well-documented risks he pointed out were the development of osteoporosis, myopathy, and oedema; the disruption of lipid and carbohydrate metabolism; and the risk of developing glaucoma and cataracts.

“The bottom line is always give as much as necessary, but as little as possible,” said Prof. Frank Buttgereit of the department of

rheumatology at Charité–Universitätsmedizin Berlin.

Over the past few years, EULAR’s Glucocorticoid Task Force has been reviewing and updating recommendations on the use of these drugs, and it has published several important documents clarifying their use in RA and in PMR. The task force has also published a viewpoint article on the long-term use of glucocorticoids, defining the conditions where an “acceptably low level of harm” might exist to enable their continued use. There have also been separate recommendations, published in 2010, on how to monitor these drugs (*Ann Rheum Dis.* 2010;69[11]:1913-9).

Clarifying the role of glucocorticoids in RA

The latest (2016) EULAR recommendations on the use of glucocorticoids were published last year (*Ann Rheum Dis.* 2017;76[6]:960-77) and

included an important adjustment on when they should be initially used in RA, Prof. Buttgereit explained. Previous recommendations had said that glucocorticoids could be combined with disease-modifying antirheumatic drugs (DMARDs) but had suggested that they be used at a low dose. Now the wording has changed to focus on short-term use rather than dosing.

“We have made it clear that glucocorticoids should really be used only when initiating conventional synthetic DMARDs, but not necessarily if you switch to biologics or targeted synthetics because usually the onset of their actions is pretty fast,” Prof. Buttgereit said.

One thing that hasn’t changed is that glucocorticoids should be tapered down as “rapidly as clinically feasible” until, ideally, their full withdrawal, although there

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are cases when that might not be possible, and their long-term use might be warranted. This is when you get into discussion about the benefit-to-risk ratio, he said.

Glucocorticoids for polymyalgia rheumatica

Glucocorticoids may be used as monotherapy in patients with PMR, Prof. Buttgerit observed, which is in contrast to other conditions such as RA. Although the evidence for use of glucocorticoids in PMR is limited, the EULAR Glucocorticoid Task Force and American College of Rheumatology recommended (Ann Rheum Dis. 2015;74[10]:1799-807) using a starting dose of a prednisolone-equivalent dose between 12.5 and 25 mg/day, and if there is an improvement in few weeks, the dose can start to be reduced. Tapering should be rapid

at first to bring the dose down to 10 mg/day and followed by a more gradual dose-reduction phase.

Balancing long-term benefit vs. harm

Balancing the long-term benefits and risks of glucocorticoids in rheumatic disease was the focus of a EULAR viewpoint article published 3 years ago in 2015 (Ann Rheum Dis. 2015;75[6]:952-7).

Three main messages can be drawn out of this work, he said.

First, treatment with glucocorticoids for 3-6 months is associated with more benefits than risks if doses of 5 mg/day or less are used. There is one important exception to this, however, and that is the use of glucocorticoids in patients with comorbid cardiovascular disease.

Second, using doses of 10 mg/day for long periods tips the balance to-

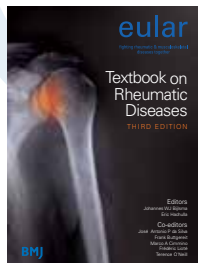
ward more risks than benefits, and "this means you should avoid this."

Third, doses of 5-10 mg/day may be appropriate, but there are certain patient factors that will influence the benefit-to-harm ratio that need to be considered. These include older age, smoking, high alcohol consumption, and poor nutrition. There are also factors that may help protect the patients from risk, such as early diagnosis, low disease activity, low cumulative dose of glucocorticoids, and a shorter duration of treatment.

"It's not only the dose, it's also the absence or presence of risk factors and/or preventive measures," that's important, Prof. Buttgerit said.

Prof. Buttgerit has received consultancy fees, honoraria, travel expenses, and/or grant or study support from many pharmaceutical companies. □

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Biologic efficacy differs in psoriatic arthritis by lymphocyte phenotype

BY TED BOSWORTH

In patients with psoriatic arthritis (PsA), new evidence suggests selection of biologic disease-modifying antirheumatic drugs (bDMARDs) might be individual-



Dr. Ippei Miyagawa

“The bDMARDs effective in PsA have different targets and may not offer the same degree of efficacy in all patients. Our study suggests an approach to optimal drug selection.”

ised by T-helper cell phenotype to improve disease control, according to the results of a study presented at the Congress.

“Our findings suggest a potential for precision medicine in patients with psoriatic arthritis,” reported Dr. Ippei Miyagawa of the University of Occupational and Environmental Health in Kitakyushu, Japan.

In this study, 26 patients were divided into four lymphocyte phenotypes based on the peripheral blood analysis. These were a CXCR3+CCR6-CD38+HLA-DR+ activated Th1 cell-predominant type (Th1 predominant), a CXCR3-CCR6+CD38+HLA-DR+ activated Th17 cell-predominant type (Th17 predominant), a Th1/Th17-high type-predominant type (Th1/Th17 high), and a Th1/Th17-low-predominant type (Th1/Th17 low).

These phenotypes were employed to individualise therapy with the currently available targeted bDMARDs. Patients with a Th1-predominant phenotype received ustekinumab, which blocks the p40 subunit of interleukin (IL)-12 and IL-23. Patients with a Th17-predominant phenotype received secukinumab, which targets IL-17. Patients with the Th1/Th17-high phenotype received either secukinumab or a tumour necrosis factor inhibitor. Patients with the Th1/Th17-low phenotype received a TNF inhibitor.

The 26 patients whose bDMARD therapy was individualised were compared with 38 PsA patients who received bDMARDs selected according to EULAR recommendations. The groups were similar for baseline characteristics.

In both groups, there were significant decreases from baseline in essentially all clinical measures, including the Simplified Disease Activity Index, the Psoriasis Area and Severity Index, and the Patient Global Health Assessment. However, several disease markers suggested greater disease control in those receiving individualised therapy. For example, the Disease

Activity Score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) at 6 months was 0.76 in the Th17-predominant group versus 1.32 in those on an unselected bDMARD therapy ($P = .008$).

As a proportion of lymphocytes, Th1-predominant cells greater than 1.2% and Th17-predominant cells greater than 1.5% appeared to be sensitive cutoffs for predicting response to ustekinumab and secukinumab, respectively, according to data presented by Dr. Miyagawa. Although the results in this small series of patients are considered preliminary, Dr. Miyagawa said, “We think that this research is the first step toward the future use of precision medicine in PsA.”

Larger studies are needed to verify that lymphocyte phenotyping is an effective and reproducible strategy for individualising selection of bDMARDs, but Dr. Miyagawa acknowledged other practical barriers to routine clinical application of this strategy. In particular, he called flow cytometry, which was employed in this study to phenotype lymphocyte expression, “complicated” for routine clinical use. However, this study strongly suggests that lymphocyte expression is a predictor of response to the different bDMARDs now available for treatment of PsA.

“The bDMARDs effective in PsA have different targets and may not offer the same degree of efficacy in all patients. Our study suggests an approach to optimal drug selection,” he said.

The study was not industry funded. Dr. Miyagawa reported no relevant financial disclosures. □

High RA biologic drug levels linked with more infections

BY MITCHEL L. ZOLER

Patients with rheumatoid arthritis who had a high serum level of biologic immunomodulatory drugs had a statistically significant 51% higher rate of infection during their first year on the drug, compared with RA patients who maintained usual or low serum levels of the same drugs, according to an analysis of 703 U.K. patients in a national database.

The results suggest that, once patients with rheumatoid arthritis go into remission on a higher dosage of biologic agents that produce a high serum level “dose tapering may lower their risk of infection,” Dr. Meghna Jani said at the Congress.

This apparent relationship between higher biologic drug levels and increased infections “may be another reason to measure drug levels in patients; it could make their treatment safer, as well as save money,” said Prof. John D. Isaacs, a professor of clinical rheumatology at Newcastle University in Newcastle upon Tyne, United Kingdom, who was a coauthor on the study.

The study used data and specimens collected in two separate, prospective U.K. studies: the British Society for Rheumatology Biologics Register-RA, which had data from more than 20,000 U.K. patients with RA who started treatment with a biologic agent, and BRAGGSS (Biologics in Rheumatoid Arthritis and Genetics and Genomics Study Syndicate), a national prospective cohort of 3,000 RA patients who had serum specimens drawn at 3, 6, and 12

months after starting biologic drug treatment and tested by an immunoassay for the concentration of the drug each patient received.

The analysis focused on 703 patients for whom there was data while they were on treatment with any of five biologic drugs: the tumour necrosis factor inhibitors adalimumab (179 patients), certolizumab pegol (120 patients), etanercept (286 patients), and infliximab (14 patients) and the interleukin-6 blocker tocilizumab (104 patients).

Dr. Jani and her associates considered serum levels that exceeded the following thresholds to categorise patients as having a high drug level: 8 mcg/mL adalimumab, 25 mcg/mL certolizumab, 4 mcg/mL etanercept, 4 mcg/mL infliximab, and 4 mcg/mL tocilizumab. The patients averaged about 59 years old, about three-quarters were women, and they had been diagnosed with RA for approximately 5-7 years. About 22% were also on treatment with a glucocorticoid, and most patients had not received prior treatment with a biologic agent.

The researchers tallied 229 diagnosed infections in the subgroup with high serum levels of their biologic drug, and 63 infections in those with levels below this threshold. After adjustment for age, sex, methotrexate use, and disease activity score, patients with high serum levels of their biologic drug had a 51% higher rate of all infections than did patients with levels that fell below the high-level threshold, reported Dr. Jani, a rheumatologist at Manchester (United Kingdom) University.

Analysis of the accumulation of infections over the course of 1 year of follow-up showed that this difference in infection rates became apparent after about 2 months of



Dr. Meghna Jani

exposure and then began to diverge more sharply after about 5 months of exposure.

The results also showed that the rate of serious infections – defined as those needing intravenous antibiotics, hospitalisation, or resulting in death – were similar in the two subgroups. The types of infections and their relative frequencies were also roughly similar in the two subgroups. Lower respiratory infections were the most common infection in both subgroups, followed by infections of the upper respiratory tract, urinary tract, and skin as the next three most common infections in both subgroups.

Dr. Jani had no relevant disclosures. Dr. Isaacs has been a consultant to several companies that market biologic drugs for treating rheumatoid arthritis. □

Glucocorticoids and biologics linked with surgical infections in RA patients

BY MITCHEL L. ZOLER

Patients with rheumatoid arthritis who underwent elective knee or hip arthroplasty had a doubled rate of hospitalisation for infection when they averaged more than 10 mg/day oral prednisone during the 3 months before surgery, based on a review of about 11,000 U.S. insurance claims.

“Limiting glucocorticoid exposure before surgery should be a focus of perioperative management,” Dr. Michael D. George said at the Congress. “Glucocorticoid use, especially greater than 10 mg/day, is associated with a greater risk of infection and hospital readmission,” said Dr. George, a rheumatologist at the University of Pennsylvania in Philadelphia.

The analysis also showed that treatment with any biologic drug – including abatacept, rituximab, tocilizumab, and any of several tumor necrosis factor (TNF) inhibitors – had a similar impact on both postsurgical infections requiring hospitalisation and 30-day hospital readmissions.

The findings suggest “it’s more important to reduce glucocorticoids than biological drugs,” commented Prof. John D. Isaacs, professor of clinical rheumatology at Newcastle University in Newcastle upon Tyne, United Kingdom. “This is a really important question that has been very difficult to answer.”

Dr. George and his associates used data from patients with rheumatoid arthritis during 2006-2015 who underwent knee or hip arthroplasty and were in databases from Medicare, or MarketScan, which includes commercial insurers. This identified 11,021 RA patients on any of several biologic drugs before their surgery: 16% on abatacept, 4% on rituximab, 4% on tocilizumab, and the remaining 76% on a TNF inhibitor, either adalimumab, etanercept, or infliximab.

About 43% of all patients were on a glucocorticoid during the 3 months before surgery. Biologic use was defined as a minimum of one dose within 8 weeks of surgery, and at least three total dosages during the prior year, except for rituximab, which was at least one dose given 16 weeks before surgery and at least two doses during the prior year.

The rate of hospitalised infections ranged from 6.6% to 8.5% depending on the biologic drug used, and 30-day readmissions ranged from 4.8% to 6.8%. A third outcome the analysis assessed was prosthetic joint infection during 1-year follow-up, which was again similar across most of the biologics, except for patients on tocilizumab, who had prosthetic joint infections roughly threefold more often than the other patients. Although this was a statistically significant difference, Dr. George discounted the finding given the very small number of tocilizumab-treated patients who had these infections and said that any conclusion about tocilizumab’s effect on this outcome had to await data from more patients.

The glucocorticoid analysis divided patients into four subgroups: those not on a glucocorticoid, those on an average daily dosage of 5 mg/day prednisone or equivalent or less, patients on 6-10 mg/day prednisone, and those on more than 10 mg/day. In a propensity-weighted analysis, these three escalating levels of glucocorticoid use showed a dose-response relationship to the rates of both hospitalised infections and 30-day readmissions. At the highest level of glucocorticoid use, hospitalised infections occurred twice as often as in patients not on a glucocorticoid, and 30-day readmissions were more than 50% higher than in those not on an oral



Dr. John D. Isaacs



Dr. Michael D. George

glucocorticoid, both statistically significant differences. For the outcome of 1-year prosthetic joint infections, the analysis again showed a dose-related link among glucocorticoid users, topping out with a greater than 50% increased rate among those on the highest glucocorticoid dosages when compared with nonusers, but this difference was not statistically significant.

The study was partially funded by Bristol-Myers Squibb (BMS), which markets abatacept. Dr. George has received research funding from BMS, which employs several of his coauthors. □

IMAGINE-RA: No need for MRI with treat-to-target strategy

BY SARA FREEMAN

Results of the IMAGINE-RA study show no added benefit of using magnetic resonance imaging as part of a treat-to-target strategy for rheumatoid arthritis.

At 2 years, similar percentages of patients achieved the coprimary endpoints of Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) remission or no radiographic progression regardless of whether MRI was used. Indeed, 85% versus 88% ($P = .958$) of patients achieved a DAS28-CRP of less than 2.6, and 66% and 62% exhibited no radiographic changes ($P = .922$) with the MRI-guided or conventional treat-to-target strategies.

“Despite patients achieving a target of clinical remission, we still see erosive progression in about 20%-30%,” study investigator Dr.

“Targeting absence of MRI bone marrow oedema in addition to a conventional treat-to-target strategy in RA patients in clinical remission had no effect on the probability of achieving DAS28-CRP remission.”

Signe Møller-Bisgaard said at the Congress. That’s regardless of the definition of remission that you use, she added.

Dr. Møller-Bisgaard, a resident in rheumatology and postdoctoral researcher who works at Rigshospitalet and Frederiksberg Hospital in Copenhagen, observed that both synovial inflammation and bone marrow oedema seen on MRI had

been shown to predict progression in patients with rheumatoid arthritis.

What was not known, however, was whether there was any value in specifically targeting MRI remission in patients who had already achieved clinical remission. This is what the IMAGINE-RA study set out to address. It was a 2-year trial of 200 patients with rheumatoid arthritis in clinical remission who were recruited and randomised to either an MRI or conventional treat-to-target strategy. The study involved nine rheumatology and eight radiological departments, Dr. Møller-Bisgaard said.

The protocol for the study (Trials. 2015;16:178) defined clinical remission as a DAS28-CRP of 3.2 or lower and no swollen joints. Patients had to have erosions on x-ray, be anti-cyclic citrullinated peptide positive, and be treated only with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) at the time of entry.

During the study, patients were assessed every 4 months via the DAS28 or DAS28 plus MRI of the dominant hand and wrist, with radiographs of the hands and feet performed annually in both groups and MRI also performed yearly in the conventional treat-to-target group.

“Treatment was intensified in both arms if the DAS28-CRP was above 3.2 and there was at least one clinical swollen joint,” Dr. Møller-Bisgaard explained. Treatment was also intensified in the MRI group if bone marrow oedema was observed. Treatment intensification involved maximal doses of csDMARDs alone or in combinations and then addition of biologic treatments, such as a tumour necrosis factor inhibitor.

“Targeting absence of MRI



Dr. Signe Møller-Bisgaard

bone marrow oedema in addition to a conventional treat-to-target strategy in RA patients in clinical remission had no effect on the probability of achieving DAS28-CRP remission or halting radiographic progression,” she said.

However, there were some positive effects on several predefined secondary endpoints. For instance, more patients in the MRI group than in the conventional treat-to-target group achieved American College of Rheumatology/EULAR remission (49% vs. 32%; $P = .017$). There was a significant improvement in the number of swollen joints and a patient and physician global assessment. “There was also more improvement in HAQ [Health Assessment Questionnaire], with a difference between the groups of .14 [P less than .001],” Dr. Møller-Bisgaard reported.

The IMAGINE-RA study is funded by grants from the Danish Rheumatism Association and the Research Fund of Region Zealand. Funding is also provided by AbbVie via a nonrestricted grant, and adalimumab is provided free of charge. Dr. Møller-Bisgaard and her coauthors had no personal conflicts of interest to declare. □

Factors prominent in delay of treatment receive attention

BY NICOLA GARRETT



Souzi Makri



Dr. Rebecca Stack

“Research indicates that patients who are treated early have better outcomes. Early treatment also can increase patient satisfaction and reduce patient stress.”

A wide range of potentially modifiable factors affect delay in treatment of rheumatic and musculoskeletal diseases, according to presentations at the Congress. These presentations focused on reasons patients postpone getting help when they first experience symptoms, whether perception and coping styles are associated with patient delay, and how the delay of treatment is seen from the patient and physician perspectives.

As with many illnesses, early diagnosis of diseases such as rheumatoid arthritis, lupus, and Sjögren's syndrome can result in improved treatment and management, which results in reduced illness disability and improved patient quality of life. But this too often is impeded by long delays between the onset of symptoms and treatment. There are two types of delay. “Patient delay” covers the period from the time when an individual realises he/she is experiencing symptoms to the scheduling of the first medical consultation. “Health care professional delay” is the period between a patient's first medical consultation and his/her referral to a rheumatologist.

Dr. Rebecca Stack of Nottingham (England) Trent University performs research on early symptom experiences of rheumatology patients and reasons for delay after onset of symptoms. Her presentation, “Reasons for delay in help seeking at the onset of symptoms,” focused on the range of biological (symptom-related), psychological, and social factors that may influence whether an individual puts off seeing a medical professional when first experiencing symptoms.

“In some cases, early symptoms may be nonspecific and associated with aging, stress, ‘over doing it,’ or other issues that a person would

not typically connect with an illness in need of medical attention,” said Dr. Stack. “As a result, patients often wait for symptoms to disappear. The symptoms may disappear completely, may reappear intermittently, or may increase in intensity.” Barriers to seeing a medical professional can include a psychological barrier to seeking help, as well as concerns about well-being, mental health, and quality of life. Other impediments include the individual's level of awareness of health issues and health literacy, as well as health inequalities and socio-economic factors.

“Research indicates that patients who are treated early have better outcomes,” Dr. Stack explained. “Early treatment also can increase patient satisfaction and reduce patient stress. Efforts to reduce the time between symptom onset and the initiation of treatment can benefit patients in a number of ways.”

“It is important that interventions are designed to increase appropriate forms of help seeking for specific rheumatologic conditions while also discouraging inappropriate behaviours associated with hypochondria and health anxiety. It's a challenge requiring a great deal of multidisciplinary research.”

Many patients lack information about rheumatologic diseases and don't recognise their symptoms, which results in delayed visits to a doctor. Physicians, in turn, may delay referral to a specialist. Each postponement can put off a diagnosis, which can result in increased patient pain and possible disability.

Souzi Makri, a patient expert and vice president of the Cyprus League Against Rheumatism (CYPLAR), discussed challenges and possible solutions during her talk “The patients perspective on

continued on following page

All good research needs a patient partner

BY NICOLA GARRETT

Underlining clear research priorities and securing funding are key, but when research gets underway, having patients' input is not just nice to have, it's imperative to having a well-rounded outcome that's relevant to the actual patient, according to Codruta Zabalan, a EULAR Patient Research Partner (PRP).

In a talk that Ms. Zabalan gave at the Congress about PRPs and patients' future involvement in research, she said that no matter how complicated the research or how brilliant the researcher, patients can always offer unique, invaluable insights.

Past experience has shown that their advice when designing, implementing, and disseminating research outcomes invariably makes studies more effective, more credible, and often more cost efficient.

Ms. Zabalan, who is a member of the Romanian League Against Rheumatism and a PRP within the Scientific Committee of the Foundation for Research in Rheumatology, said this idea was captured beautifully by the following quote from the researchers and PRPs participating in the INVOLVE project in 2009: "Patients are

the best and only source of patient experience information. We have the experience and skills that complement the researchers. We know what it feels like to suffer a particular disease and to undergo the treatments with their various side effects. We have a good idea of which research questions are worth asking and when a question should be framed differently. We contribute by making research more socially relevant."

In 2009, EULAR established a network of educated PRPs – defined as persons with a relevant disease who operate as active research team members on an equal basis with professional researchers, adding the benefit of their experiential knowledge to any phase of the project.

Since 2010, there have been three EULAR courses to train patients to become research partners. There are now 59 trained PRPs within the EULAR Network.

The network has developed supportive materials such as reference cards and a background brochure for researchers and PRPs.

According to Ms. Zabalan, EULAR-trained PRPs are highly sought after and she already has



Codruta Zabalan

been approached to become a PRP within an Innovative Medicines Initiative project called Rheuma Tolerance for Cure (RTCure).

"The positive experience of EULAR PRP network, OMERACT PRP network (and all other worldwide networks) should make policy makers, funders, and researchers acknowledge the fact that participatory research is imperative for achieving the best outcome in research, producing relevant health benefits," Ms. Zabalan said. □

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delay in treatment."

"When patients delay getting care, it can result in continuous pain, fatigue, joint stiffness, deformations, depression, and disability," noted Ms. Makri. "The issue is important because postponed treatment not only deprives patients of having a good quality of life but also forces some of them to stay out of the workforce. This results in a social cost, including productivity losses."

Ms. Makri aimed at exposing health professionals to the perspective of the patient, which can help them recognise symptoms and re-

fer individuals to a rheumatologist during the early disease stages. Her talk also illustrated the need for a team approach to the management of rheumatic and musculoskeletal diseases, along with timely and personalised treatment. It reiterated to patients the importance of being informed, which will allow them to seek medical attention at the soonest possible date.

Many challenges in delay of treatment exist, including the importance of raising public awareness about symptoms, seeking early treatment, and educating general practitioners to make timely referrals, Ms. Makri said. She said that part of the solu-

tion lies in media public awareness campaigns, use of EULAR's "Don't Delay, Connect Today" campaign, patient self-management training, and general practitioner education from patient experts.

"The best rheumatologic disease treatment is provided by a team of health care professionals due to multifaceted nature of these illnesses," Ms. Makri concluded. "The team should work in close collaboration with the patient, who needs to be informed and educated, allowing him or her to participate in shared treatment decision making."

Dr. Stack and Ms. Makri had no disclosures of interest. □

Patients with RMDs need physical and psychological support at work

BY HEIDI SPLETE

Individuals who have a rheumatic and musculoskeletal disease (RMD) face challenges in all areas of their lives, including the workplace, and health professionals can play a key



Erika Mosor

“In recent years, different kinds of prevention programmes have been conducted for people with RMDs in the workplace. However, the number of reported physical and psychosocial problems in daily routine is still high.”

role in enabling these patients’ participation in the workforce, according to Erika Mosor of the Medical University of Vienna.

At the Congress, Ms. Mosor addressed the importance of being

able to work on RMD patients’ health and well-being.

“As people affected by RMDs often have problems in participating in work, they should be supported by health professionals to stay in their jobs or return to work and education,” Ms. Mosor said in an interview. “In recent years, different kinds of prevention programmes have been conducted for people with RMDs in the workplace. However, the number of reported physical and psychosocial problems in daily routine is still high,” she said.

Common challenges faced by individuals with RMDs in the workplace setting include pain and fatigue that impact their ability to work. For example, many patients experience physical limitations that prevent them from carrying out certain duties, and many need more breaks and longer rest periods during the day and while completing a task, Ms. Mosor said. RMD patients may not always receive adequate support from supervisors and colleagues as they struggle with these challenges, she noted.

“Therefore, people with RMDs need access to adequate rheumatology services that provide the right care at the right time,” said Ms. Mosor. “In addition, health professionals in rheumatology aim to provide individuals with the knowledge and skills to make informed life and work decisions and support people with RMDs to stay in – or return to – work and education,” she said.

Ms. Mosor advised that targeted preventive workplace interventions should focus on reducing the impact of diseases, reducing disability, and limiting or delaying complications. “People with RMDs

should be engaged in work and enjoy long and productive careers in a variety of occupations as long as they need to and want to,” she said.

Ms. Mosor recommended a variety of strategies and interventions to empower patients with RMDs in the work environment, including taking breaks for rest or exercises, arranging an ergonomic workspace and equipment, using assistive devices and equipment as needed, establishing options such as flexible work hours and working from home, and assistive equipment such as customised hand splints, as well as counseling to help patients deal with the emotional strain of managing their disease at work.

“However, health professionals should be aware of the differences in individuals, the environment, and the diversity of occupations when providing support,” Ms. Mosor said. “Ideally, interventions and modifications should be selected and evaluated together with the person with RMD,” she emphasised.

Additional research is needed to determine the most effective support systems for patients with RMDs in the workplace, Ms. Mosor said. “Future studies should involve people with RMDs and all other stakeholders when evaluating the development, the implementation, feasibility, and outcome of workplace interventions and programmes. Furthermore, mixed-methods designs would allow exploring the patient perspectives on workplace interventions in more detail,” she added.

Ms. Mosor had no financial conflicts to disclose. □

Ankylosing spondylitis progression slowed when NSAIDs added to TNFi

BY TED BOSWORTH

When combined with a tumour necrosis factor inhibitor (TNFi), NSAIDs provide protection against long-term radiographic progression in patients with ankylosing spondylitis, according to an analysis of more than 500 patients presented at the Congress.

“The greatest effect is really in those patients using celecoxib and TNFi,” reported Dr. Lianne S. Gensler, director of the Ankylosing Spondylitis Clinic at the University of California, San Francisco.

Relative to TNFi alone, the addition of NSAIDs of any type provided protection at 4 years against radiographic progression as measured with the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). However, the protection associated with adding celecoxib was significant at 2 years and greater than that of adding nonselective NSAIDs at 4 years.

These data were drawn from 519 patients participating in the Prospective Study of Ankylosing Spondylitis. All patients in this analysis were followed for at least 4 years. Radiographs were obtained every 6 months.

Although the study was a retrospective analysis of prospectively collected data, Dr. Gensler explained that control of variables such as disease and symptom duration with a technique called causal interference modeling “allows simulation of a randomised, controlled trial with observational data.”

Whether measured at 2 or 4 years, the reductions in mSASSS score for TNFi use versus no TNFi use were modest and did not reach

statistical significance. However, exposure to NSAIDs plus TNFi did reach significance at 4 years, and the effect was dose dependent when patients taking a low-dose NSAID, defined as less than 50% of the index dose, were compared with those taking a higher dose. In this study, 70% were on chronic NSAID therapy, and these patients were divided relatively evenly between those on a low-dose or high-dose regimen.

At 2 years, relative radiographic protection with TNFi plus NSAIDs was not significantly greater than with TNFi alone, but at 4 years, the median mSASSS score was 1.24 points lower (*P* less than .001) in those receiving low-dose NSAIDs and 3.31 points lower (*P* less than .001) in those receiving high-dose NSAIDs.

In the subgroup of patients taking high-dose NSAIDs, the protection from progression was greatest among those receiving the selective COX2-inhibitor celecoxib. In these, the median 3.98 points lower mSASSS score (*P* less than .001) was already significant at 2 years. At 4 years, the median mSASSS score in those receiving TNFi plus celecoxib was 4.69 points lower (*P* less than .001).

Further evaluation suggested that the benefit from celecoxib plus TNFi was not just additive but synergistic, according to Dr. Gensler. She reported that neither TNFi nor celecoxib alone provided radiographic protection at 2 or 4 years.

Despite the modelling strategy employed to reduce the effect of bias, Dr. Gensler acknowledged that residual confounding is still possible. But she contended that



Dr. Lianne S. Gensler

“a large effect [from a such a variable] would be required to negate the findings.”

One of the messages from this study is that “not all NSAIDs are alike,” Dr. Gensler said. “Despite this, when I sit with a patient across from me, I will still treat the patient based on symptoms and disease activity first, though perhaps choose to be more NSAID selective if this is warranted and feasible.”

The next steps for research include a randomised, controlled trial combining TNFi and varying NSAIDs or different doses, Dr. Gensler said. In addition, “the development of newer imaging modalities will allow us to answer these questions in a more feasible time frame.”

The study was not industry funded. Dr. Gensler reported financial relationships with Amgen, AbbVie, Janssen, Eli Lilly, Novartis, and UCB. □



ROBERT LODGE/MD EDGE NEWS

VIDEO HIGHLIGHTS: [Click here](#) to watch a video interview with Dr. Daniel H. Solomon, a professor of medicine at Harvard Medical School and a rheumatologist at Brigham and Women's Hospital, both in Boston.

Canakinumab cut gout attacks in CANTOS

BY MITCHEL L. ZOLER

Treatment with the anti-inflammatory, interleukin-1–blocking drug canakinumab roughly halves gout attacks in an exploratory, post hoc analysis of data collected from more than 10,000 patients in the CANTOS multicentre, randomised trial.

While this result is only a hypothesis-generating suggestion that blocking interleukin (IL)-1 beta can have a significant impact on the frequency of gout flares, it serves as a proof-of-concept that IL-1 beta blockade is a potentially clinically meaningful strategy for future efforts to block gout attacks, Dr. Daniel H. Solomon said at the Congress.

“IL-1 beta is incredibly important in the inflammation associated with gout. Gout is considered by many to be the canonical IL-1 beta disease,” and hence it was important to examine the impact that treatment with the IL-1 beta blocker canakinumab had on gout in the CANTOS trial, Dr. Solomon ex-

plained in a video interview.

The answer was that treatment with canakinumab was linked with a roughly 50% reduction in gout flares in the total study group. The same reduction was seen in both the subgroups of patients with and without a history of gout. The effect was seen across all three subgroups of patients, based on their baseline serum urate levels, including those with normal, elevated, or very elevated levels, and across all the other prespecified subgroups, including divisions based on sex, age, baseline body mass index, and baseline level of high-sensitivity C-reactive protein (hsCRP).

It's also unclear that canakinumab is the best type of IL-1 beta blocking drug to use for prevention of gout flares. In CANTOS, this expensive drug was administered subcutaneously every 3 months. A more appropriate agent might be an oral, small-molecule drug that

blocks IL-1 beta. Several examples of this type of agent are currently in clinical development, said Dr. Solomon, a professor of medicine at Harvard Medical School and a rheumatologist at Brigham and Women's Hospital, both in Boston.

CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) randomised 10,061 patients with a history of MI and a hsCRP level of at least 2 mg/L at centres in 39 countries. The study's primary endpoint was the combined rate of cardiovascular death, MI, or stroke, and canakinumab treatment at the 150-mg dosage level linked with a 15% relative reduction in this endpoint, compared with placebo, in this secondary-prevention study (N Engl J Med. 2017 Sept 21;377[12]:1119-31). The study also randomised patients to either of two other canakinumab dosages, 50 mg or 300 mg, administered

continued on following page

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every 3 months, and while each of these produced reductions in the primary endpoint relative to placebo, the 150-mg dosage had the largest effect. In the gout analysis reported by Dr. Solomon, the three different canakinumab dosages produced somewhat different levels of gout-flare reductions, but generally, the effect was similar across the three treatment groups.

In the total study population, regardless of gout history, treatment with 50 mg, 150 mg, and 300 mg canakinumab every 3 months was linked with a reduction in gout attacks of 46%, 57%, and 53%, respectively, compared with placebo-treated patients, Dr. Solomon reported. The three dosages also uniformly produced significant drops in serum levels of hsCRP, compared with placebo,

but canakinumab treatment had no impact on serum urate levels, indicating that the gout-reducing effects of the drug did not occur via a mechanism that involved serum urate.

Because CANTOS exclusively enrolled patients with established coronary disease, the new analysis could not address whether IL-1 beta blockade would also be an effective strategy for reducing gout flares in people without cardiovascular disease, Dr. Solomon cautioned. Although it probably would, he said. He also stressed that treatment with an IL-1 blocking drug should not be seen as a substitute for appropriate urate-lowering treatment in patients with elevated levels of serum urate.

CANTOS was funded by Novartis, the company that markets canakinumab. Dr. Solomon has no rela-

Because CANTOS exclusively enrolled patients with established coronary disease, the new analysis could not address whether IL-1 beta blockade would also be an effective strategy for reducing gout flares in people without cardiovascular disease.

tionships with Novartis. Brigham and Women's Hospital, the centre at which he works, has received research funding from Amgen, Bristol-Myers Squibb, Genentech, and Pfizer for studies that Dr. Solomon has helped to direct. □

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Ultrasound aids treat-to-target approach for gout

BY SARA FREEMAN

Results from the longitudinal NOR-GOUT study show that ultrasound can help visualise decreases of uric acid deposits that occur during a treat-to-target approach with urate-lowering therapy.

Ultrasound-detected crystal depositions decreased over the course of the 1-year study for all three ultrasound signs considered, researcher Dr. Hilde B. Hammer reported at the Congress.

“Gout is a really painful disease when there are flares,” said Dr. Hammer, a senior consultant in the rheumatology department at Diakonhjemmet Hospital in Oslo. Ultrasound has been shown to be a sensitive method to detect uric monosodium urate (MSU) deposition, and its use is included in the classification criteria for gout.

“MSU depositions are found in many different regions with some predilection sites,” Dr. Hammer noted. This led the OMERACT (Out-

come Measures in Rheumatology) Ultrasound Group to develop three key definitions for MSU lesions: the “double contour sign” (DC), which occurs when urate crystals form on the surface of cartilage; “tophus,” in which there is a larger, hypoechoic aggregation of crystals that is usually well delineated; and “aggregates,” which are small, hyperechoic deposits.

“There are, up until now, only a few smaller studies that have explored the decrease of depositions during uric acid-lowering treatment,” Dr. Hammer observed.

NOR-GOUT was a prospective, observational study of 161 consecutively-recruited patients with urate crystal-proven gout who needed treatment with urate-lowering therapy. Patients were included if they had a recent gout flare and had serum urate levels of more than 360 micromol/L and had no contraindication to urate-lowering therapy.

“We used a treat-to-target approach with the medication,” Dr. Hammer explained. The aim was to get uric acid levels to 360 micromol/L or lower or to less than 300 micromol/L if clinical tophi were present. “The medication was optimised by monthly follow-up by a study nurse until the treatment target was met,” she added.

Patients underwent an extensive ultrasound assessment at study entry and again after 3, 6, and 12 months of urate-lowering therapy. This included bilateral assessment of all relevant joints and the presence of crystals semiquantitatively scored from 0 to 3, the latter sig-

nifying many deposits. The sum of scores for the three key OMERACT definitions were calculated each time the patients were assessed, with a total score for all three also calculated.

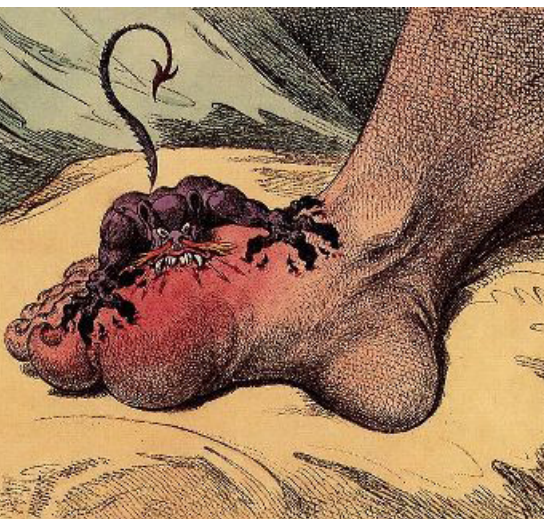
Mean serum urate levels dropped from a baseline of 487 to 312 micromol/L at 12 months (*P* less than .001), Dr. Hammer reported. The percentage of patients achieving a urate target of less than 360 micromol/L increased from 71% at 3 months to 81% at 6 months and to 84% at 12 months, she said.

Ultrasound scores decreased with decreasing urate levels at 3, 6, and 12 months, with the highest numeric difference from baseline seen at 12 months for DC (3.1, 2.3, and 1.2; all *P* less than .001 vs. baseline of 4.2). The respective values for tophi were 6.3, 5.4, and 4.2 versus a baseline of 6.5; for aggregates, the values were 8.8, 7.9, and 6.7 versus a baseline of 9.1.

Standardised Response Mean values from baseline to 3, 6, and 12 months showed that DC was the most sensitive for change, with a respective 0.73, 1.02, and 1.26 in ultrasound scores. Values for tophi were 0.06, 0.57, and 0.91 and 0.20, 0.51 and 0.66 for aggregates.

“Not all patients had reached 12 months of follow-up when we made these calculations,” Dr. Hammer said, noting the limitations of the study. Nevertheless, these interim findings suggest that ultrasound is a valuable tool that can help see how patients fare on a treat-to-target approach, she concluded.

Dr. Hammer had no conflicts of interest to disclose. □



Podagra: The Gout
By James Gillray (1799)

Bisphosphonate 'holidays' exceeding 2 years linked to increased fractures

BY MITCHEL L. ZOLER

Older women on bisphosphonate treatment for at least 3 years who then stopped taking the drug showed a 40% increased risk for hip fracture after they were off the bisphosphonate for more than 2 years, compared with women who never stopped using the drug, according to an analysis of more than 150,000 women in a Medicare database.

The implication of this observational-data finding is that drug holidays from a bisphosphonate regimen "may not be appropriate for all patients," Dr. Kenneth G. Saag said at the Congress.

"Drug holidays [from a bisphosphonate] have become increasingly common" because of concerns about potential adverse effects from prolonged, continuous bisphosphonate treatment, especially the risk for osteonecrosis of the jaw and atypical femoral fractures, noted Dr. Saag, a rheumatologist and professor of medicine at the University of Alabama at Birmingham, USA. These bisphosphonate stoppages are sometimes permanent and sometimes temporary, he said. Ideally, assessment of the risks and benefits from a bisphosphonate drug holiday should occur in a randomised study, but in current U.S. practice, such a trial would be "impossible because there is not equipoise around the decision of whether or not to stop," he said.

To try to gain insight into the impact of halting bisphosphonate treatment with observational data, Dr. Saag and his associates used records collected by Medicare on 153,236 women who started a new course of bisphosphonate treatment and remained on it for at least 3 years during 2006-2014. When selecting these women, the researchers also focused on those with at least 80% adherence

to their bisphosphonate regimen, based on prescription coverage data. The analysis censored women who also received other treatments that can affect bone density, such as oestrogen or denosumab. The average age of the women was 79 years; two-thirds were aged 75 years or older. The median duration of bisphosphonate treatment in the studied cohort before the drug use stopped was 5.5 years, and follow-up continued for a median of 2.1 years. Forty percent of the women stopped their bisphosphonate treatment for at least 6 months, and 13% of the women who stopped treatment subsequently restarted a bisphosphonate drug. The most commonly used bisphosphonate was alendronate, used by 72%, followed by zoledronic acid, used by 16%.

The analysis divided women who stopped their bisphosphonate treatment into subgroups based on the duration of stoppage, and this showed that the rate of hip fracture was 40% higher among women who stopped treatment for more than 2 years but not more than 3 years, compared with the women who never interrupted their bisphosphonate treatment, a statistically significant difference, Dr. Saag said. In contrast, among women who halted bisphosphonate treatment for more than 1 year but not more than 2 years, the hip fracture risk was 20% higher than that of nonstoppers, also a statistically significant difference. These and all the other analyses the researchers ran adjusted for the possible impact from baseline differences in several demographic and clinical variables.

Dr. Saag cautioned that while the relatively increased risk for hip fracture from a prolonged halt to



MITCHEL L. ZOLER/MEDICAL NEWS

Dr. Kenneth G. Saag

bisphosphonate treatment was 40%, the absolute increase in risk was "relatively modest," representing an increased fracture rate of 0.5-1 additional fractures during every 100 patient-years of follow-up.

For the endpoint of major osteoporotic fracture at any location, the risk was 10% higher among women who stopped treatment for more than 2 years but not for longer than 3 years, compared with nonstoppers.

The researchers also focused on two key subgroups. Among women who only took alendronate, a drug holiday of more than 2 years was linked with a statistically significant 20% rise in hip fractures, compared with women who never stopped the drug. And among the 4% of studied women who had a history of a bone fracture because of bone fragility, stoppage of their bisphosphonate treatment for more than 2 years doubled their hip fracture rate, compared with similar women who did not stop their treatment.

The study received no commercial funding. Dr. Saag has been a consultant to and has received research funding from Amgen, Lilly, and Radius. □

Checkpoint inhibitors in autoimmune disease: More flares, better cancer outcomes

BY TED BOSWORTH

In patients with autoimmune diseases, cancer treatment with checkpoint inhibitor immunotherapy increases the risk of flares, but these flares are associated with improved cancer outcomes, according to a multicentre, retrospective study presented at the Congress.

“Survival was longer in patients who experienced a flare of their preexisting autoimmune disease or any other immune-related adverse event, but this gain was lost if an immunosuppressive therapy was used,” reported Alice Tison, a resident in rheumatology at the Centre Hospitalier Universitaire, Brest, France.

These were some of the mixed messages from this evaluation, which involved 112 patients with preexisting autoimmune disease (PAD) whose data were collected from 11 tertiary care centres in France. Of the cases of PAD represented, the majority involved joint diseases, including psoriatic arthritis (28%), rheumatoid arthritis (18%), and spondyloarthritis (4.5%). However, other types of PAD, including inflammatory bowel disease (13%), were included in the series.

Only 33% of the patients had active disease at the time that checkpoint inhibitor therapy was initiated, and only 21% were taking an immunosuppressive therapy for their disease. Of those on therapy, the majority were taking glucocorticoids, but about a third of those on therapy were taking a disease-modifying antirheumatic drug, such as methotrexate.

With the initiation of checkpoint inhibitors, which were offered primarily for the treatment of melanoma (59%) and non-small cell lung cancer (36%), 42% of patients with



Alice Tison

PAD developed a disease flare. Of these, 30% were considered severe. Other immune-related events not considered related to the underlying disease, such as colitis, were also observed but at rates not clearly different than those observed in patients without PAD.

The activity of checkpoint inhibitors did not appear to be different than that observed in non-PAD patients. For example, the overall response rate was 48% in those with melanoma and 54% in those with non-small cell lung cancer. After a median of 8 months of follow-up, the median progression-free survival was 12.4 months and 9.7 months for the two diseases, respectively. Median overall survival had not been reached in either disease.

However, those with a flare or another immune-related adverse event had significantly better progression-free survival ($P = .016$) and overall survival ($P = .004$) when compared with those who did not flare or have an immune-related adverse event. According to Ms. Tison, this has been reported before, but a more surprising finding was that the gain

in progression-free survival and overall survival was lost in those treated with an immunosuppressive drug.

Even though non-PAD patients commonly receive glucocorticoids for immune-related adverse events such as colitis, the loss of benefit in PAD patients who received immunosuppressive therapies may be caused by, at least in part, cross-reactivity between tumour antigens and autoantigens, Ms. Tison speculated.

Ms. Tison was cautious in drawing conclusions about specific strategies to optimise benefits from checkpoint inhibitors in PAD based on this limited series of patients. However, she did suggest that discontinuation of immunosuppressive therapies prior to initiating checkpoint inhibitors may be prudent in PAD patients, particularly those with inactive disease.

Overall, she emphasised that checkpoint inhibitors “have revolutionised the management of several cancers” and should not be denied to PAD patients who are otherwise appropriate candidates. Although flares are common, more than half of PAD patients in this series did not flare and flares were mild to moderate in most of those who did.

“The response to checkpoint inhibitors in PAD patients is good,” Ms. Tison advised. For those who do flare, “we need prospective studies to understand which strategies provide a good balance of benefit to risk” for cancer immunotherapy and for the options to manage immune-related adverse events.

The study was not industry funded. Ms. Tison reported no potential conflicts of interest. □

Malignancy risk of tocilizumab and TNF inhibitors found similar

BY TED BOSWORTH

Tocilizumab poses no greater risk for malignancy than do tumour necrosis factor inhibitors (TNFis) in the treatment of rheumatoid ar-



Dr. Seoyoung C. Kim

thritis, according to an analysis of three large databases presented at the Congress.

“When we combined the databases, the incidence of any malignancy excluding nonmelanoma skin cancer was 13.09 per 1,000 patient-years in the tocilizumab group and 13.46 in the TNF-inhibitor group,” reported Dr. Seoyoung C. Kim of the division of pharmacoepidemiology & pharmacoecconomics at Brigham and Women’s Hospital, Boston.

This difference, reflected in a cancer hazard ratio of 0.98 (95% confidence interval, 0.80-1.19) for tocilizumab versus TNFis, did not approach statistical significance.

The study was conducted with data from 10,393 adult RA patients treated with tocilizumab

and 26,357 patients treated with TNFis in the Medicare, Quintiles-IMS PharMetrics Plus, and Truven Health MarketScan databases.

All patients were new starts on tocilizumab or the TNFi on which they were evaluated, but all were required to have been exposed to at least one different biologic prior to starting the treatment. A diagnosis of RA at least 365 days prior to inclusion in this analysis was required to rule out prevalent cancers, which was an exclusion criterion.

More than 60 covariates were employed in the analysis to minimize the risk of confounders. These included demographics, RA characteristics, comorbidities, and other medications.

There also was no difference in the rates of the 12 most common cancer types when those exposed to tocilizumab were compared with those exposed to TNFis in a secondary analysis of these data, according to Dr. Kim. When expressed as hazard ratios, there were some numerical differences in relative risk among these cancers on both as-treated and intention-to-treat analyses, but confidence intervals were large, and none approached significance.

RA itself has been associated with an increased risk of some malignancies, such as lung cancer, but the relationship between the proinflammatory state of RA, its treatments, and the risk of cancer has been unclear, according to Dr. Kim. She said, “There is some concern relative to use of TNFis or other biologics in regard to developing malignancy, but studies have been inconsistent.”

Dr. Kim conceded that a lack of

data on patients’ disease duration or activity is one limitation of this analysis. Another is that residual confounding can never be ruled out from a retrospective analysis. However, she said that, because the two biologics were compared for the same indication in patients exposed to at least one previous biologic, the confounding may be less than it would be if tocilizumab were compared with a conventional synthetic disease-modifying antirheumatic drug, such as methotrexate. Again, there also was a requirement for exposure to at least one prior biologic, and this also is reassuring for the final conclusion.

“In other words, even among RA patients who were exposed to more than one biologic, the risk of cancer was similar between tocilizumab and TNF-inhibitor initiators,” Dr. Kim reported.

Roche provided funding for the study. Dr. Kim reported having financial relationships with Bristol-Myers Squibb, Pfizer, and Roche. □

“When we combined the databases, the incidence of any malignancy excluding nonmelanoma skin cancer was 13.09 per 1,000 patient-years in the tocilizumab group and 13.46 in the TNF-inhibitor group,” which did not approach statistical significance.

Functional disability prevails despite rheumatoid arthritis treatment

BY SARA FREEMAN

Functional disability remains a significant problem for people with rheumatoid arthritis, with the prevalence remaining at least 15% higher over time than in individuals without the disease.



Dr. Elena Myasoedova

In a retrospective, longitudinal, population-based cohort study, the prevalence of patient-reported functional disability was 26% in 586 individuals with rheumatoid arthritis and 11% in 531 without the disease at baseline (P less than .001), a discrepancy that persisted over almost 20 years of follow-up.

“We found a higher prevalence of functional disability in patients with RA versus non-RA,” the presenting study investigator Dr. Elena Myasoedova said at the Congress.

Dr. Myasoedova, who is a clinical fellow in rheumatology at the Mayo Clinic in Rochester, USA, added that the increase in prevalence over time was significantly higher in subjects with RA than in those without RA ($P = .003$), but that there was no difference in the pace of this increase with adjustment for the duration of RA disease ($P = .51$).

There was also no difference in functional disability between the

two groups of patients by about the 8th or 9th decade.

RA remains one of the most common conditions associated with functional disability, Dr. Myasoedova said, with several risk factors for physical impairment identified, including being female, of older age, smoking, and the use of certain medications (glucocorticoids and antidepressants), as well as sociodemographic factors.

A discrepancy between improved RA disease control and persistent impairment in physical function has been noted in prior studies, but there are few data on how this might change over time. Dr. Myasoedova and her associates investigated this by analysing data from the Rochester Epidemiology Project, which collects medical data on individuals living in Olmsted County, Minnesota, USA. They identified two populations of adults aged 18 and older: one diagnosed with RA according to 1987 American College of Rheumatology criteria between 1999 and 2013 and one without RA but who were of a similar age and sex and enrolled in the project around the same time.

As part of the project, participants completed an annual questionnaire asking about their health and ability to perform six activities of daily living (ADL). These include the ability to wash, dress, feed, and toilet oneself without assistance, as well as perform normal household chores and walk unaided. Over the course of the study, 7,466 questionnaires were completed by the participants, and functional disability was defined as having difficulty with at least one of these six ADLs, Dr. Myasoedova explained.

At baseline, subjects with and

without RA were aged a mean of 55 and 56 years, respectively, and 70% in both groups were female. Similar percentages were current (about 15%), former (about 30%), or never smokers (about 55%), and about 40% were obese.

Just under two-thirds (64.4%) of patients in the RA cohort were positive for rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibodies. While there was a similar prevalence of functional disability in RA patients who were or were not RF or anti-CCP positive (both 25%, $P = .67$), there was an increasing prevalence in those who were positive versus those who were negative over time ($P = .027$).

Although the investigators did not conduct an objective assessment for functional disability, these findings highlight the need for vigilant management of patients with RA, Dr. Myasoedova proposed.

“Early and aggressive treatment regimens aimed at tight inflammation control can help prevent the disabling effects of high disease activity and joint damage, thereby lowering functional disability,” she said in an interview ahead of the Congress.

Future work, she observed, should look at how the pattern of functional disability changes and the use of transition modeling to understand the bidirectional pattern of potential change and accumulation of functional disability in RA. The investigators also plan to look at risk factors for persistent and worsening functional disability and how treatment – including treat to target and biologics – might affect this.

The U.S. National Institute of Arthritis and Musculoskeletal and Skin Diseases supported the study. Dr. Myasoedova had no conflicts of interest. □

Synovial tissue changes arise before RA

BY HEIDI SPLETE

Seropositive individuals at risk for rheumatoid arthritis developed synovial tissue changes at the molecular level long before developing the disease in a study presented at the Congress.

“Early detection of RA-associated autoantibodies now enables identification of individuals at risk to develop RA in order to study the molecular and cellular processes driving disease development,” said first author Dr. Lisa van Baarsen of the Amsterdam Rheumatology and Immunology Center. But “not all autoantibody-positive, RA-risk individuals develop disease, suggesting that other, yet unidentified factors play a role.”

However, Dr. van Baarsen added that “it is unknown where inflammatory events that lead to RA are initiated. Earlier microscopy-based studies from our department showed no overt cellular infiltration in the synovium of RA-risk individuals before onset of disease.”

The investigators studied 67 adults who were positive for IgM rheumatoid factor and/or anti-citrullinated protein antibody but had no evidence of arthritis. All participants underwent miniarthroscopic synovial biopsy sampling of a knee joint at baseline.

The researchers conducted an explorative, genome-wide, transcriptional profiling study on synovial biopsies from 13 of the individuals, and 6 of these developed RA after an average of 20 months’ follow-up. The genomic analysis showed that individuals who developed RA had greater expression

of genes involved in several immune response-related pathways, such as T-cell and B-cell receptor pathways, cytokine and chemokine signalling, and antigen processing and presentation, compared with those who did not develop RA.

“Although our earlier studies did not indicate increased cellular infiltration in the synovium of pre-RA individuals, I was not surprised to identify an increased expression of genes involved in immune responses since the adaptive immune response is activated in these autoantibody-positive individuals,” Dr. van Baarsen said. “I was surprised to identify synovial alterations in lipid metabolism, which deserves further investigation,” she noted.

The researchers used survival analysis to identify transcripts showing a significant association with arthritis development.

With a false discovery rate of less than 5%, the increased expression of 3,151 transcripts correlated with a higher risk of arthritis development, and increased expression of 2,437 transcripts correlated with a lower risk. By contrast, individuals who developed RA showed lower expression of genes involved in extracellular matrix receptor interaction, Wnt-mediated signal transduction, and lipid metabolism.

“Subsequently, the expression level of a selection of 27 differentially expressed genes was validated by quantitative real-time PCR [polymerase chain reaction] in 61 RA-risk individuals,” the researchers said.

“Although this study has no immediate implications for clinical practice, it revealed that the target tissue of RA, the synovium, is changing already during the preclinical phase of disease,” Dr.



Dr. Lisa van Baarsen

van Baarsen said. “Studying these synovial changes further may lead to the discovery of innovative drug targets and lay the foundation for preventive intervention.”

Next steps for research include investigating the function of the resident stromal cells during the preclinical phase of RA and “how we can restore or use their tolerogenic capacity,” Dr. van Baarsen added.

Dr. van Baarsen had no financial conflicts to disclose. Several co-authors are employees of GlaxoSmithKline, but the company had no role in this study. □

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