IN BRIEF

SJÖGREN SYNDROME

CD40 blockade shows promise in pSS trial

Iscalimab, an anti-CD40 monoclonal antibody, showed preliminary efficacy for the treatment of primary Sjögren syndrome (pSS) in a phase II placebo-controlled trial ($n = 44$). Of the two administration routes tested (intravenous and subcutaneous), only intravenous iscalimab resulted in a significant reduction in the EULAR Sjögren's syndrome disease activity index (ESSDAI) score after 12 weeks of treatment compared with placebo (95% CI 0.96–9.46; one-sided $P = 0.0090$). Only two severe adverse events were reported across all groups, neither of which was related to iscalimab.

ORIGINAL ARTICLE Fisher, B. A. et al. Assessment of the anti-CD40 antibody iscalimab in patients with primary Sjögren's syndrome: a multicentre, randomised, double-blind, placebo-controlled, proof-of-concept study. *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(19)30135-3 (2020)

OSTEOARTHRITIS

Knee OA increases risk of all-cause mortality

Analysis of data on 4,796 participants from the Osteoarthritis Initiative has revealed an increased risk in all-cause mortality in individuals with knee osteoarthritis (OA). Compared with individuals with no knee pain and no radiographic knee OA, individuals with symptomatic knee OA (pain and radiographic progression) had a hazard ratio (HR) for mortality of 2.2 (95% CI 1.6–3.1), whereas those with radiographic OA had an HR of 2.0 (95% CI 1.4–2.9), and those with knee pain only had an HR of 0.9 (95% CI 0.6–1.4). Disability and changes in quality of life related to OA partly contributed to the increase in mortality.

ORIGINAL ARTICLE Wang, Y. et al. Knee osteoarthritis, potential mediators, and risk of all-cause mortality: data from the Osteoarthritis Initiative. *Arthritis Care Res.* https://doi.org/10.1002/acr.24151 (2020)

SYSTEMIC LUPUS ERYTHEMATOSUS

Risk variant in long noncoding RNA linked to SLE

The results of a GWAS of long noncoding RNAs (lncRNAs) in Han Chinese individuals that included 4,556 patients with systemic lupus erythematosus (SLE) have revealed a new SLE risk locus (rs13259960) in a lncRNA termed SLE-associated RNA (SLEAR). The new risk variant causes a reduction in the amount of SLEAR that is produced in an individual. In vitro analyses suggest that SLEAR regulates apoptosis, a process associated with the pathogenesis of SLE. Furthermore, patients with SLE with the rs13259960 variant had a reduced amount of SLEAR, which correlated with an increase in T cell apoptosis.

ORIGINAL ARTICLE Fan, Z. et al. The polymorphism rs13259960 in *SLEAR* predisposes to systemic lupus erythematosus. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41200 (2020)

SPONDYLOARTHRITIS

Long-term safety of ixekizumab confirmed in PsA

No unexpected safety signals were found in an integrated analysis of data from three clinical trials of ixekizumab in patients with psoriatic arthritis (PsA). Exposure to ixekizumab over 1,822.2 patient years was evaluated across data from the SPIRIT-P1, SPIRIT-P2 and SPIRIT-P3 trials. The incidence rates for serious adverse events and serious infections remained stable over time, whereas the incidence rates for general infections and injection-site reactions decreased with exposure to ixekizumab. The main opportunistic infections reported were herpes zoster and oral or oesophageal *Candida*.

ORIGINAL ARTICLE Combe, B. et al. Safety results of ixekizumab with 1822.2 patient-years of exposure: an integrated analysis of 3 clinical trials in adult patients with psoriatic arthritis. *Arthritis Res. Ther.* **22**, 14 (2020)

FIBROINFLAMMATORY DISORDERS

International classification criteria created for IgG_4-related disease

IgG_4-related disease, an immune-mediated fibroinflammatory disorder that can affect multiple organs, has only been recognized as a distinct disease since 2003. The varied manifestations and organ systems involved make it a difficult disease to study and have necessitated the creation of an international set of classification criteria, endorsed by both the American College of Rheumatology (ACR) and EULAR.

A group of 86 physicians from North America, Europe, Asia and Australia worked together to identify potential classification criteria and to provide derivation and validation cohorts of patients with IgG_4-related disease (n = 1,086) and diseases that mimic this condition (n = 793).

"The research group included rheumatologists, internists, ophthalmologists, pathologists, gastroenterologists, allergists, pulmonologists, radiologists, neurologists, nephrologists, and a variety of other subspecialists," says principal investigator John Stone. "The enthusiasm and collegiality among investigators was a source of inspiration to the group overall, and a major contributor to the overall success of the effort."

An initial set of 51 exclusion criteria and 27 inclusion criteria was refined by the ability of each criterion to distinguish between IgG_4-related disease and mimicking conditions. The use of exclusion criteria was particularly remarkable, as most classification criteria rely on inclusion criteria alone.

"For a disease that is as protean as IgG_4-related disease and as capable of mimicking (and being mimicked by) so many other conditions, exclusion criteria were an important part of our effort," explains Stone. "The specificity of the overall ACR–EULAR classification criteria were improved by about 10% simply by the use of exclusion criteria."

The final inclusion criteria were designed to avoid the absolute need for a biopsy to reach a conclusion of IgG_4-related disease, although most patients will require one. A patient must have either characteristic involvement (clinical or radiological) or pathological evidence of inflammation in a typically affected organ, not meet any of the exclusion criteria and accrue a total of 20 points or more from the weighted inclusion criteria to be classified as having IgG_4-related disease. Typical organs include the pancreas, salivary glands, lungs, kidneys, bile ducts, aorta, retroperitoneum, thyroid gland, orbits and pachymeninges.

"The two independent validation studies we performed demonstrated remarkably consistent results: an extremely high specificity (>98%) and a high sensitivity (85%)," enthuses Stone. "The final criteria set is easy to use and lends itself well to adaptation in an electronic format, which we have already instituted at my hospital."

Stone and colleagues are keen to remind researchers that the ACR–EULAR classification criteria, while informative in a clinical setting, are not designed for diagnosis. Not all patients with IgG_4-related disease will be captured by the criteria owing to their design, but the authors hope that they can be successfully used to recruit cohorts of patients with relatively homogeneous disease for clinical and epidemiological studies, which will aid research efforts.

"It is essential that studies include patients who truly merit classification as having IgG_4-related disease. These rigorous ACR–EULAR classification criteria will help guide us through some of the most important challenges of studying this disease well," concludes Stone.

Joanna Clarke

ORIGINAL ARTICLE Wallace, Z. S. et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG_4-related disease. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2019-216561 (2019)