IN BRIEF

RHEUMATOID ARTHRITIS

Early referral matters for RA outcomes

Among patients with a diagnosis of rheumatoid arthritis (RA) in the Leiden Early Arthritis Clinic and the French ESPOIR cohorts followed for 7–10 years, those who first met with a rheumatologist within 6 weeks of symptom onset were more likely to achieve sustained DMARD-free remission than those who were seen by a rheumatologist 7–12 weeks after symptom onset (HR 1.69; 95% CI 1.10–2.57) or more than 12 weeks after symptom onset (HR 1.67; 95% CI 1.08–2.58). Radiographic progression was more severe in those not seen within 12 weeks of symptom onset, but was similar in the other two groups.

ORIGINAL ARTICLE Niemantsverdriet, E. et al. Referring early arthritis patients within 6 weeks versus 12 weeks after symptom onset: an observational cohort study. *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(20)30061-8 (2020)

SYSTEMIC LUPUS ERYTHEMATOSUS

Increased risk of infection-related death in SLE

In a retrospective study using the National Health Insurance Fund of Hungary database, the rate of death was higher in adults with systemic lupus erythematosus (SLE) than in matched individuals without SLE (standardized mortality ratio (SMR) 1.63; 95% CI 1.43–1.83) and even higher in the subgroup of patients with SLE who had received treatment within the first 6 months of diagnosis (SMR 2.09; 95% CI 1.80–2.39). Infection-related deaths were more common in the patients with SLE compared with the non-SLE group, attributable largely to an increased frequency of sepsis being the cause of death in the patients with SLE.

ORIGINAL ARTICLE Kedves, M. et al. Large-scale mortality gap between SLE and control population is associated with increased infection-related mortality in lupus. *Rheumatology* https://doi.org/10.1093/rheumatology/keaa188 (2020)

SPONDYLOARTHRITIS

Anti-TNF response falls short in real-world cohort

In a study of participants in the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS), 51.3% of those with axial spondyloarthritis (axSpA) commencing treatment with TNF inhibitors reported a positive response, a lower proportion than that reported in clinical trials (61.7%). Compared with the real-world BSRBR-AS cohort, participants in the clinical trials were more likely to be male, HLA-B27 positive and younger (by approximately 6 years). Disease activity was similar in both groups but the BSRBR-AS participants reported poorer function prior to commencing treatment.

ORIGINAL ARTICLE Jones, G. T. et al. Real-world evidence of TNF inhibition in axial spondyloarthritis: can we generalise the results from clinical trials? *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2019-216841 (2020)

VASCULITIS

MMF comparable to cyclophosphamide in AAV

As a remission induction therapy in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), the therapeutic efficacy of mycophenolate mofetil (MMF) is similar to that of cyclophosphamide, according to a meta-analysis of data from four randomized controlled trials. In the studies, which enrolled a total of 300 patients with AAV, MMF and cyclophosphamide led to similar rates of remission at 6 months, ANCA negativity at 6 months and long-term relapse. Rates of death among patients with AAV were similar with both treatments.

ORIGINAL ARTICLE Kuzuya, K. et al. Efficacy of mycophenolate mofetil as a remission induction therapy in antineutrophil cytoplasmic antibody: associated vasculitis — a meta-analysis. *RMD Open* **6**, e001195 (2020)

RHEUMATOID ARTHRITIS

Disease onset goes with its gut in RA

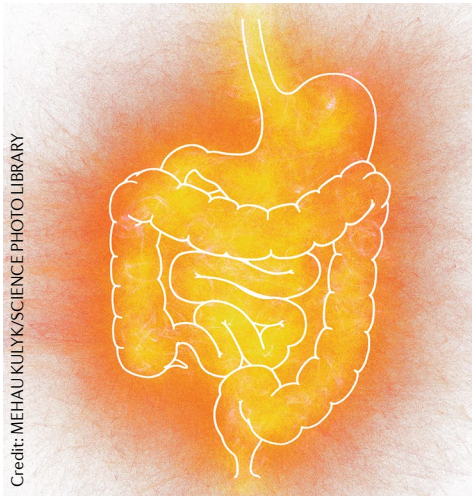
The mucosal origins hypothesis postulates that, in rheumatoid arthritis (RA), disease begins to develop at mucosal sites such as the gums, lungs and intestines and then transitions to involve synovial joints. Links between gut microbiota dysbiosis and RA, and between dietary intake of short-chain fatty acids (SCFAs) and autoimmune arthritis in mice, have provided support for this hypothesis, but a direct link between mucosal sites and the transition from systemic autoimmunity to arthritis has been missing.

A new study published in *Nature Communications* has revealed a role for intestinal barrier function, and specifically for zonulin, a precursor of haptoglobin 2 that controls epithelial tight junction permeability, in regulating the onset of joint disease in mice with collagen-induced arthritis (CIA) and potentially also in patients with RA.

Mice with CIA had increased intestinal permeability in the period between the induction of autoimmunity and the onset of clinical symptoms, which corresponded with a rise in serum zonulin. This reduction in intestinal barrier function was accompanied by an influx of effector T cells in the small intestine. Interestingly, arthritis only developed in mice that had this increased intestinal permeability.

Reducing intestinal permeability in the period before clinical arthritis, either by dietary supplementation with the SCFA butyrate, treatment with a selective intestinal cannabinoid receptor 1 agonist (cannabinoid receptor 1 regulates intestinal epithelial barrier function) or treatment with larazotide acetate (which blocks zonulin and is currently in phase III clinical trials for coeliac disease) delayed disease onset and reduced the severity of arthritis.

"The most significant finding is that improving the intestinal barrier function in mice with non-clinical CIA positively affects subsequent disease onset and severity," states corresponding author Mario Zaiss. "These results relate nicely to data published very recently by other groups showing mucosal inflammation in animal models of arthritis, and complete these interesting studies by providing a treatment opportunity."



Credit: MEHAU KULYK/SCIENCE PHOTO LIBRARY

In a cohort of patients with RA-specific autoimmunity but no clinical symptoms (described as pre-RA), Zaiss and colleagues found evidence of intestinal barrier dysfunction and an increase in serum zonulin concentrations that correlated with the risk of developing RA. These results imply that zonulin could be studied further as a biomarker to predict disease onset in patients with pre-RA.

"Similar intestinal phenotypes could be found in individuals with pre-RA to those present in mice with CIA, and as improving the intestinal barrier function had clinical relevance on subsequent disease onset and severity in mice, we are currently planning the first studies to translate these findings to humans," says Zaiss.

Joanna Clarke

ORIGINAL ARTICLE Tajik, N. et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. *Nat. Commun.* **11**, 1995 (2020)