IN BRIEF

OSTEOPOROSIS

Biosimilar for teriparatide safe and effective

The biosimilar RGB-10 had a similar safety and efficacy profile to reference teriparatide in a phase III head-to-head study in a Japanese cohort of patients with osteoporosis at high risk of fracture. 250 patients were randomly allocated on a 1:1 basis to receive daily subcutaneous injections of either 20 µg RGB-10 or 20 µg teriparatide for 52 weeks. The change in lumbar spine bone mineral density from baseline to week 52 was equivalent between the two treatment groups and no major differences in adverse events were reported. RGB-10 is currently approved for use in the same indications as teriparatide in the EU.

ORIGINAL ARTICLE Hagino, H. et al. A multicenter, randomized, rater-blinded, parallel-group, phase 3 study to compare the efficacy, safety, and immunogenicity of biosimilar RGB-10 and reference once-daily teriparatide in patients with osteoporosis. *Osteoporos. Int.* https://doi.org/10.1007/s00198-019-05038-y (2019)

OSTEOARTHRITIS

Mother–daughter inheritance patterns in OA

The results of a risk estimation study suggest that the inheritance of osteoarthritis (OA) potentially occurs through the maternal line. The risk of OA was assessed in relation to family history of OA in participants from the Norwegian MUST and Nor-Twin OA studies ($n = 630$ and $n = 7{,}175$, respectively). Having a mother with OA consistently increased the risk of OA of any type in daughters (relative risk $(RR)_{MUST}$ 1.13, 95% CI 1.02–1.25; $RR_{Nor\text{-}Twin}$ 1.44, 95% CI 1.05–1.97) and to a lesser degree in sons (RR_{MUST} 1.16, 95% CI 0.95–1.43; $RR_{Nor\text{-}Twin}$ 1.31, 95% CI 0.71–2.41). By contrast, having a father with OA did not increase the risk of OA of any type in either daughters or sons.

ORIGINAL ARTICLE Weldingh, E. et al. The maternal and paternal effects on clinical and surgical definitions of osteoarthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41023 (2019)

SYSTEMIC LUPUS ERYTHEMATOSUS

Epstein–Barr virus reactivation linked to SLE

In a cohort of 436 relatives of patients with systemic lupus erythematosus (SLE), reactivation of Epstein–Barr virus (EBV) and polymorphisms in EBV-related genes were associated with the eventual development of SLE (average follow-up of 6.3 years). In the 56 individuals who developed SLE, titres of antibodies against EBV antigens (indicative of EBV reactivation) were increased compared with titres in those who did not develop SLE. Polymorphisms in *CD40* and *IL10* were also associated with increased titres of antibodies against EBV antigens in individuals who developed SLE.

ORIGINAL ARTICLE Jog, N. R. et al. Association of Epstein-Barr virus serological reactivation with transitioning to systemic lupus erythematosus in at-risk individuals. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2019-215361 (2019)

OSTEOARTHRITIS

Anti-NGF therapy improves osteoarthritis pain

The anti-nerve growth factor (NGF) antibody fasinumab improved pain and function in patients with osteoarthritis (OA) in a phase III study in the USA. 342 patients with knee or hip OA were randomly allocated on a 1:1:1:1:1 basis to receive either placebo, or fasinumab at 1 mg, 3 mg, 6 mg or 9 mg doses, every 4 weeks for 16 weeks. All doses of fasinumab produced statistically significant and clinically important reductions in pain compared with placebo at 16 weeks. One patient receiving 6 mg fasinumab developed destructive arthropathy.

ORIGINAL ARTICLE Dakin, P. et al. The efficacy, tolerability and joint safety of fasinumab in osteoarthritis pain: a phase IIb/III double-blind, placebo-controlled, randomized clinical trial. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41012 (2019)

PAIN

Neuronal Fcγ receptors mediate joint pain in arthritis

Autoantibodies contribute to joint pain by binding to Fcγ receptors (FcγRs) expressed on sensory neurons, even in the absence of inflammation, according to evidence from two new studies.

In one study, Lintao Qu and colleagues showed that IgG immune complexes (IgG-ICs) activate joint sensory neurons in an FcγRI-dependent manner. In wild-type mice, local administration of IgG-ICs induced acute joint pain without obvious inflammation. Notably, this pronociceptive effect was diminished in *Fcgr1*$^{-/-}$ mice and in mice with conditional knockout of *Fcgr1* in sensory neurons. "These conditional knockout mice allow us to unambiguously dissect the contributions of neuronal versus non-neuronal FcγRI to arthritis pain and define the neuronal subtypes involved," explains Qu.

Next, using a model of antigen-induced arthritis (AIA), Qu and colleagues demonstrated that FcγRI signalling is upregulated in sensory neurons in mice with AIA. Pain-related behaviour was attenuated in *Fcgr1*$^{-/-}$ as compared with wild-type mice over the course of AIA, but with no differences between the two genotypes in the occurrence of joint inflammation. Furthermore, in wild-type mice with AIA, pharmacological blockade of FcγRI by local injection of anti-CD64 antibody reduced established arthritis pain but not joint inflammation. Together, the results provide evidence of the contributions of peripheral IgG-IC–FcγRI signalling to joint pain, independent of inflammation, in both naive and arthritic states. "These findings could define a promising candidate therapeutic target for patients with pain arising from rheumatoid arthritis or other autoimmune-related diseases in whom anti-inflammatory therapies are inadequate, unaffordable or poorly tolerated," says Qu.

In a separate study, Rikard Holmdahl, Camilla Svensson and their collaborators explored the mechanisms by which antibodies with reactivity to cartilage induce pain in the collagen-antibody-induced arthritis (CAIA) model. They observed that injection of antibodies against type II collagen (CII) or to cartilage oligomeric matrix protein (COMP) induced a pain response in mice before the onset of signs of joint inflammation, independently of the complement cascade or changes in cartilage structure. Notably, intra-articular injection of CII immune complexes (CII-ICs) induced pain-like behaviour in wild-type mice, but not in FcRγ-chain deficient mice. The researchers also established that the pronociceptive effect of anti-CII antibodies requires both epitope recognition and interaction between immune complexes and FcγRs on neurons. Through a series of further experiments, the researchers determined that the critical FcR for the development of immune-complex-mediated pain-like behaviour was neuronal FcγRI, consistent with the results of the study by Qu et al.

"From a medical viewpoint, this study explains why arthralgia develops before the onset of clinical arthritis during the onset of RA. From the physiological viewpoint, it gives us an explanation for how antibodies aggregating in a specific tissue could activate peripheral nociceptors," says Svensson.

"We want to expand our work to examine if local formation of immune complexes is a general mechanism of pain in rheumatic and autoimmune diseases. Such insights would give us a new angle on how to prohibit the development of pain that is caused by antibodies," adds Holmdahl.

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ORIGINAL ARTICLES Wang, L. et al. Neuronal FcγRI mediates acute and chronic joint pain. *J. Clin. Invest.* https://doi.org/10.1172/JCI128010 (2019) | Bersellini Farinotti, A. et al. Cartilage-binding antibodies induce pain through immune complex-mediated activation of neurons. *J. Exp. Med.* https://doi.org/10.1084/jem.20181657 (2019)