IN BRIEF

OSTEOPOROSIS

Denosumab shows promise for GIOP

In a double-blind study, the monoclonal antibody denosumab was both non-inferior and superior to the bisphosphonate risedronate for the treatment of glucocorticoid-induced osteoporosis (GIOP). Patients were randomly assigned to receive 60 mg denosumab subcutaneously every 6 months ($n = 398$) or 5 mg oral risedronate daily ($n = 397$); both groups also received placebo. At 12 months, denosumab had greater effects than risedronate on bone mineral density at the lumbar spine both in patients who were already using glucocorticoids (4.4% versus 2.3%; $P < 0.0001$) and in those initiating glucocorticoid therapy (3.8% versus 0.8%; $P < 0.0001$).

ORIGINAL ARTICLE Saag, K. G. et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol.* https://doi.org/10.1016/S2213-8587(18)30075-5 (2018)

AUTOIMMUNITY

Triple therapy boosts survival in catastrophic APS

Combined therapy with anticoagulation and glucocorticoids plus plasma exchange and/or intravenous immunoglobulins improves the survival rate of patients with catastrophic antiphospholipid syndrome (APS), according to data from an international registry. Triple therapy was associated with a higher chance of survival in comparison with treatment with other combinations of the drugs included in the triple therapy (adjusted OR 1.7, 95% CI 1.2–2.6) or treatment with none of those drugs (adjusted OR 9.7, 95% CI 2.3–40.6).

ORIGINAL ARTICLE Rodríguez-Pintó, I. et al. The effect of triple therapy on the mortality of catastrophic anti-phospholipid syndrome patients. *Rheumatology*. https://doi.org/10.1093/rheumatology/key082 (2018)

THERAPY

Obesity hampers effects of anti-TNF agents

The results of a systematic review and meta-analysis suggest that obesity hampers the efficacy of some biologic DMARDs in the treatment of inflammatory diseases including rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis. Compared with non-obese patients (BMI ≤30 kg/m^2), obese patients (BMI >30 kg/m^2) with RA treated with an anti-TNF agent were less likely to achieve a good response (OR 0.34, 95% CI 0.18–0.64) or remission (OR 0.36, 95% CI 0.21–0.59) and those with axSpA were less likely to achieve ≥50% improvement in the BASDAI score (OR 0.41, 95% CI 0.21–0.83). The response to treatment with abatacept or tocilizumab did not differ between obese and non-obese patients.

ORIGINAL ARTICLE Juan, S. & Jiabi, Z. Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: a systematic review and meta-analysis. *Joint Bone Spine* https://doi.org/10.1016/j.jbspin.2018.03.007 (2018)

IMAGING

Flares not linked to ultrasound findings in JIA

Abnormal ultrasonography findings were common in children with clinically inactive juvenile idiopathic arthritis (JIA; $n = 40$) but did not correlate with disease flares during up to 2 years of follow-up in a single-centre study. At baseline, 45% of the patients had at least one abnormal finding on ultrasonography. These baseline findings had a sensitivity of 15% and a positive predictive value of 12% when evaluated against clinical flares at the individual joint level during follow-up.

ORIGINAL ARTICLE Zhao, Y. et al. Flares of disease in children with clinically inactive juvenile idiopathic arthritis were not correlated with ultrasound findings. *J. Rheumatol.* https://doi.org/10.3899/jrheum.170681 (2018)

Credit: Katya Ulitina/Alamy Stock Photo

GOUT

Surprising safety outcomes of urate-lowering therapy

Febuxostat is noninferior to allopurinol with respect to rates of adverse cardiovascular events in patients with gout and cardiovascular disease, according to results from a new, double-blind trial. However, in this trial, febuxostat was also associated with a higher risk of all-cause and cardiovascular mortality than allopurinol.

Gout is associated with an increased risk of cardiovascular disease and is characterized by increased levels of circulating serum urate (hyperuricaemia), which can be managed with urate-lowering therapies such as allopurinol and febuxostat. "A small increase in cardiovascular events had been observed during the development of febuxostat compared with allopurinol," remarks corresponding author William B. White. "This imbalance led to a concern among regulators in the USA and a large cardiovascular outcome study was mandated," he continues.

To determine whether febuxostat was non inferior to allopurinol, the CARES trial was conducted. In this trial, 6,190 patients with gout and a history of major cardiovascular disease were randomly assigned to receive either febuxostat or allopurinol, and were followed for a median of 32 months. "Of note, the dose of allopurinol was higher in the study than typically used in clinical practice but adjusted for renal dysfunction," explains White. "This strategy resulted in much closer serum uric acid levels for the two treatment groups."

By the end of the study, the primary outcome — a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and urgent revascularization for unstable angina — had occurred in a similar proportion of patients in both groups: 10.8% of patients in the febuxostat group and 10.4% of patients in the allopurinol group. "Unexpectedly, the rate of cardiovascular death (and all-cause mortality) was significantly higher in the febuxostat group compared with in the allopurinol group," explains White. This surprising finding was confirmed in a prespecified analysis of the events that occurred during treatment or within 30 days after treatment discontinuation, although the underlying mechanisms were unclear.

White says that his group is currently performing additional analyses on patient subgroups to evaluate the effects of various factors (such as co-administration of medications, drug dosage, rates of gout flare and baseline kidney function) on cardiovascular end points and mortality. "These analyses might further our understanding of the benefit to risk ratio of febuxostat in special patient populations with gout," explains White.

"This study will influence gout management guidelines [and] there is now a need to reconsider where febuxostat sits in the order of urate-lowering therapies," states rheumatologist Lisa Stamp, who was not involved in the study. "Physicians need to discuss the risks and benefits of any urate-lowering drug with patients and make a shared decision about which therapy is best for an individual patient. This study adds some support to using allopurinol at higher doses than many physicians would currently use to obtain target urate levels," she concludes.

Jessica McHugh

ORIGINAL ARTICLE White, W. B. et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N. Engl. J. Med.* **378**, 1200–1210 (2018)