Medicom International Conference Series in Rheumatology

ACR 2025 Congress

American College of Rheumatology

24-29 OCTOBER 2025 • CHICAGO • USA

HIGHLIGHTS
CONFERENCE REPORT

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Editor Conflict of Interest: no conflicts.

MEDICOM MEDICAL PUBLISHERS

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Advances in Inflammatory and Degenerative Rheumatic Diseases

Two-year treatment with upadacitinib shows high remission in patients with giant cell arteritis

Upadacitinib 15 mg treatment compared with placebo switch led to higher rates of complete remission and lower rates of flares, with increased rates of herpes zoster and bone fractures, according to an analysis presented by Prof. Wolfgang Schmidt (Medical Centre for Rheumatology Berlin-Buch, Germany) [1].

Patients with giant-cell arteritis in the phase 3 trial SELECT-GCA (NCT03725202) received ≥52 weeks of upadacitinib 15 mg daily, 7 mg daily, or placebo, with tapering of their baseline glucocorticoid treatment [2]. In period 2 of the trial, participants were re-randomised to their original upadacitinib dose or placebo if they received upadacitinib, while placebo participants continued with placebo for an additional 52 weeks. Outcomes included disease flares (recurrence of signs/symptoms or erythrocyte sedimentation rate >30mm/h requiring initiation of glucocorticoids) and complete remission rates (no signs/symptoms, no glucocorticoid use, normalisation of the erythrocyte sedimentation rate, and normalisation of high-sensitivity C-reactive protein). In total, 181 participants were included [1].

Assessments were carried out 30 days after the 104-week treatment period ended. Significantly more participants who switched from upadacitinib 15 mg to placebo had ≥1 disease flare than those on continuous upadacitinib 15 mg treatment (59.1% vs 15.5%; P<0.0001). Furthermore, the time to first disease flare was longer with continuous upadacitinib than placebo switch (P<0.0001). Additionally, significantly more participants receiving continuous upadacitinib 15 mg than those who switched from upadacitinib 15 mg to placebo achieved complete remission after 104 weeks of treatment (71.9% vs 20.0%; P<0.0001). Safety assessments compared continuous upadacitinib 15 mg with continuous placebo. Overall, there were increased rates of bone fractures and herpes zoster with upadacitinib.

"There is a lower risk of flare and higher rates of remission if you continue upadacitinib compared with placebo," concluded Prof. Schmidt. "There were no new clinically significant safety signals, and the results demonstrate a favourable benefit-risk profile for upadacitinib 15 mg in giant cell arteritis."

1. Schmidt W, et al. Efficacy and safety of upadacitinib in giant cell arteritis: 2-year results from the re-randomized, double-blind SELECT-GCA phase 3 trial. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.
2. Blockmans D, et al. N Engl J Med. 2025;392(20):2013-2024.

GLP-1 receptor agonists may protect against cardiac events in patients with psoriatic arthritis

Patients with psoriatic arthritis who received GLP-1 receptor agonists are at a lower risk of developing major adverse cardiovascular events than those not treated with these agents, with an added benefit of lower risk of death.

Dr Nanuka Tsibadze (Jefferson Einstein Hospital, PA, USA) reported data from an observational, retrospective study using electronic health record information from the TriNetX database [1]. Patients were included in the analysis if they were aged 18 years or older and had a diagnosis of psoriatic arthritis between January 2015 and December 2024. Two cohorts were based on use versus non-use of GLP-1 receptor agonists (semaglutide, liraglutide, exenatide, and lixisenatide). Matching between the 2 cohorts was performed based on age, sex, race, medical diagnoses, and therapy use (cardiovascular agents, insulin, and therapies for psoriatic arthritis). The primary outcome was the incidence of major adverse cardiovascular events.

In total, database analysis identified 4,104 patients with psoriatic arthritis receiving GLP-1 receptor agonists and 86,432 patients not receiving GLP-1 receptor agonists. Following matching, a total of 3,303 patients were included in each cohort. Regarding outcomes, patients with psoriatic arthritis receiving GLP-1 receptor agonists had a lower risk of developing ischemic heart disease (RR 0.715; 95%CI 0.610-0.838), cerebrovascular diseases (RR 0.605; 95%CI 0.494-0.740), acute myocardial infarction (RR 0.578; 95%CI 0.434-0.769), cerebral infarction (RR 0.633; 95%CI 0.457-0.876), heart failure (RR 0.703; 95%CI 0.618-0.799), or death (RR 0.307; 95%CI 0.222-0.425).

"Patients with psoriatic arthritis treated with GLP-1 receptor agonists might have a lower risk for developing major adverse cardiovascular events and reduced mortality compared with those not receiving GLP-1 receptor agonists," concluded Dr Tsibadze. "GLP-1 receptor agonists may be a promising adjunct therapy in the management of patients with inflammatory arthritis, but we need further prospective trials to better understand the mechanisms underlying these outcomes."

1. Tsibadze N, et al. Mortality and major adverse cardiac events (MACE) with GLP-1 receptor agonists in psoriatic arthritis. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

A urinary tenascin-C biomarker score predicts long-term kidney function in lupus nephritis

Various criteria for proteinuria are used in clinical trials for lupus nephritis. Still, they do not always correlate with long-term preservation of kidney function because they do not account for the disease's inflammatory component. A urine-based proteomic score using tenascin-C and other protein biomarkers accurately predicted long-term kidney function loss, independent of proteinuria criteria.

Dr Andrea Fava (Johns Hopkins University, MD, USA) presented results from an Accelerating Medicines Partnership study in patients with lupus nephritis, followed for a median of 4.9 years (maximum 7.8 years) [1]. Around 1,200 urinary biomarkers were analysed and compared with kidney biopsy data to determine the risk of eGFR decline (≥40%).

In total, 170 patients were followed up and divided into 2 groups: those with stable eGFR (69%) and those with a sustained eGFR decline of ≥40% (31%). Multiple biomarkers, including inflammatory and fibrosis-associated markers, were associated with sustained eGFR loss at 3, 6, and 12 months, with tenascin-C showing the highest hazard ratio for kidney function loss. A protein-based predictive score (tenascin-C plus 10 other urinary proteins) was developed to stratify patients into high- and low-risk groups for eGFR loss. This classification was significantly associated with eGFR loss (P<0.0001), both in patients considered responders (<0.5 mg/mg) and non-responders (≥0.5 mg/mg) by proteinuria criteria.

"We found that tenascin-C predicts kidney function loss in lupus nephritis," concluded Dr Fava. "The proteomic score outperforms proteinuria and helps stratify patients regardless of the current definition of response. These findings provide insight into the disease's mechanistic aspects and support the development of biomarkers to personalise treatment. Clinical trial endpoints and response definitions should be selected among biomarkers most strongly associated with eGFR protection."

1. Lee CY, et al. Urinary tenascin C predicts kidney function loss in lupus nephritis. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

LEVI-04 holds potential to be the first disease-modifying therapy for knee osteoarthritis

LEVI-04 is a neurotrophin-3 inhibitor that significantly improved pain and function compared with placebo, though with increased adverse reactions during administration, in a phase 2 trial in patients with knee osteoarthritis [1]. Dr Simon Westbrook (Levicept Ltd, UK) presented additional data focusing on bone marrow lesions [2].

LEVI-04 (NCT05618782), a phase 2, randomised trial enrolling participants with symptomatic knee osteoarthritis (WOMAC pain ≥4/10 and Kellgren-Lawrence grade ≥2) who received intravenous LEVI-04 0.3, 1, or 2 mg/kg every 2 weeks or placebo. The analysis focused on the effect of treatment on bone marrow lesions (assessed by MRI). In total, 518 participants were enrolled in the trial.

Between 70% and 77% of participants presented with a bone marrow lesion at baseline. Following 20 weeks of treatment, significantly fewer participants with LEVI-04 1 mg/kg (46%) and 2 mg/kg (39%) had bone marrow lesions, compared with no change in the placebo group (72%). Furthermore, there was a significant, dose-dependent decrease in the total average bone marrow lesion area with LEVI-04 compared with placebo. Finally, this dose-dependent decrease in bone marrow lesion area was observed across all Kellgren-Lawrence grade subgroups (2, 3, and 4).

"Our phase 2 data showed statistically significant effects on analgesia and notable effects on stiffness and pain, but also demonstrated that a proportion of the analgesia and stiffness improvement is associated with the regression of bone marrow lesions," concluded Dr Westbrook. "LEVI-04 holds promise as potentially the first therapy to modify structural signs and symptoms of osteoarthritis."

1. Conaghan P, et al. LEVI-04, a novel neurotrophin-3 inhibitor, substantially improves pain and function without deleterious effects on joint structure in people with knee osteoarthritis: A randomized controlled phase II trial. ACR Convergence, 14–19 November 2024, Washington, DC, USA.
2. Westbrook S, et al. LEVI-04 significantly reduces bone marrow lesions and symptoms in knee osteoarthritis: Results from a phase II RCT ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

A joint ASAS/SPARTAN initiative proposes revised diagnostic criteria for axial spondyloarthritis

The 2009 ASAS criteria for the diagnosis of axial spondyloarthritis are based on radiographic imaging/MRI, as well as genetic and clinical features of the disease, and have a sensitivity and specificity of 82.9% and 84.4%, respectively [1]. Prof. Walter P. Maksymowych (University of Alberta, AB, Canada) presented the results of CLASSIC, a combined initiative of ASAS and SPARTAN aimed at validating the performance of the 2009 ASAS criteria [2].

Participants were included in the Classification in Axial Spondyloarthritis Inception Cohort Study (CLASSIC) if they were referred to a rheumatologist with undiagnosed chronic back pain occurring before 45 years of age, with ≥3 months' duration, and with suspicion of axial spondyloarthritis [2]. Global assessments were conducted to validate the criteria using clinical assessment, laboratory analyses, pelvic radiographs, local MRI, and a centralised review of imaging data. A prespecified sensitivity of ≥75% and specificity of ≥90% was used to select diagnostic criteria. A total of 1,015 participants from 61 centres in 27 countries were included.

Following central review of data, 36.4% of participants in the cohort were diagnosed with axial spondyloarthritis. Several diagnostic models were proposed based on imaging, genetic, and clinical criteria. The model reaching the highest specificity (sensitivity of 79.5% and specificity of 90.4% for local readers) was based on a score ≥11, calculated as the sum of the following:

- MRI indicating axial spondyloarthritis (8) or radiographic sacroiliitis (7)
- HLA-B27 positivity (4)
- Inflammatory back pain (3)
- Peripheral arthritis (1)
- Inflammatory bowel disease (1)
- Acute anterior uveitis (1)
- Heel enthesitis (1)
- Elevated C-reactive protein (1)
- Psoriasis (1)

The adoption of these revised criteria was voted on by joint ASAS-SPARTAN members and was accepted by 158 votes in favour, 151 against, and 9 abstentions.

1. Maksymowych WP, et al. Ann Rheum Dis. 2009;68(6):777-83.
2. Maksymowych WP, et al. The assessments in Spondyloarthritis International Society (ASAS) and Spondyloarthritis Research and Treatment Network (SPARTAN) revised classification criteria for axial spondyloarthritis: Development and validation in the Classification in Axial SpA Inception Cohort Study. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Novel Immunotherapies and Targeted Treatments

Phase 2b data show that rosnilimab is effective in rheumatoid arthritis

Rosnilimab, a monoclonal antibody that selectively depletes pathogenic PD-1 high T cells, showed improvements in disease activity with acceptable safety compared with placebo in participants with moderate-to-severe rheumatoid arthritis.

Prof. Paul Emery (University of Leeds, UK) presented data from the multicentre, randomised, double-blind, phase 2b RENOIR trial (NCT06041269) in adults with rheumatoid arthritis [1]. Participants were included if they had seropositive rheumatoid arthritis, ≥6 swollen and ≥6 tender joints, high-sensitivity C-reactive protein (hs-CRP) ≥3 mg/L, and were receiving 1 or 2 disease-modifying antirheumatic drugs (DMARDs) initiated ≥3 months prior, but were excluded if they had failed ≥3 DMARDs. Randomisation (1:1:1:1) was carried out to subcutaneous rosnilimab 100 mg every 4 weeks, 400 mg every 4 weeks, 600 mg every 2 weeks, or placebo. A potential extension of 16 weeks was allowed for rosnilimab participants. The primary endpoint was the change in Disease Activity Score 28 with CRP (DAS28-CRP) from baseline to week 12. In total, 424 participants were randomised.

All doses of rosnilimab met the primary endpoint, with mean changes from baseline of -2.06, -2.12, and -2.06 for the 100 mg, 400 mg, and 600 mg arms, respectively, compared with -1.69 for placebo (P<0.01). Additionally, all rosnilimab doses led to higher proportions of participants achieving ACR20 compared with placebo. Participants who entered the extended treatment period showed sustained responses in multiple efficacy outcomes. Overall, rosnilimab was well tolerated, with discontinuation rates similar to those in the placebo group. Opportunistic infections were lower with rosnilimab than with placebo, but 1 major cardiovascular adverse event was reported in a rosnilimab-treated participant. There were no malignancies or deaths.

"In summary, the primary endpoint of mean change from baseline in DAS28-CRP was achieved across all doses of rosnilimab versus placebo, as was ACR20," concluded Prof. Emery. "Safety data through week 38 demonstrated that rosnilimab was well tolerated, with no malignancies or deaths."

1. Graf J, et al. Rosnilimab, a selective and potent depleter of pathogenic T cells, demonstrates efficacy, safety, and translational proof of mechanism in a rheumatoid arthritis phase 2b trial. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Deucravacitinib holds promise for patients with psoriatic arthritis

Deucravacitinib, a selective tyrosine kinase 2 (TYK2) inhibitor, demonstrated significant improvements versus placebo in psoriatic arthritis, with a favourable safety profile and maintenance of response over 52 weeks of treatment.

Prof. Philip Mease (Swedish Medical Center, WA, USA) presented data from the POETYK PsA-1 trial (NCT04908202), a phase 3 global, randomised, double-blind, clinical trial in participants with psoriatic arthritis [1]. Adult participants were eligible if they had ≥3 swollen joints, ≥3 tender joints, high-sensitivity C-reactive protein (hs-CRP) ≥3 mg/L, and ≥1 psoriatic arthritis-related hand or foot erosion on radiography, and were required to be biological disease-modifying antirheumatic drugs (DMARD)-naïve. Randomisation (1:1) was carried out to deucravacitinib 6 mg once daily or placebo for 16 weeks, after which participants initially receiving placebo were switched to deucravacitinib, for a total treatment duration of 52 weeks. The primary endpoint was the proportion of participants achieving an ACR20 response at week 16. In total, 670 participants were enrolled.

The trial met its primary endpoint, with ACR20 response rates of 54.2% for deucravacitinib and 34.1% for placebo (P<0.0001). Following the treatment switch, ACR20 response continued to improve, reaching 63.1% in participants who received continuous deucravacitinib and 60.8% in those who switched from placebo to deucravacitinib at week 52. Furthermore, significant improvements in ACR50 and ACR70 were observed at week 16, with responses maintained through week 52.

After 52 weeks of treatment, the most commonly reported adverse events were upper respiratory tract infection, nasopharyngitis, and hypertension. Acne was also reported in both groups, but there were no serious infections, malignancies, or major adverse cardiovascular events.

"We saw that multiple domains of psoriatic arthritis were improved through week 16 and were maintained through week 52," concluded Prof. Mease. "Furthermore, participants who were originally on placebo and switched to deucravacitinib had similar response trajectories over time. The safety profile was benign, and this oral medication will be a welcome addition to the armamentarium."

1. van der Heijde D, et al. Efficacy and safety of deucravacitinib up to Week 52: A multicenter, randomized, double-blind, placebo-controlled, phase 3 study in patients with active psoriatic arthritis who are naive to biologic disease-modifying antirheumatic drugs. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Phase 3 data reinforce ianalumab activity in Sjögren's disease

Ianalumab, a monoclonal antibody that depletes B cells through enhanced antibody-dependent cellular cytotoxicity and separately inhibits their activation through B-cell activating factor (BAFF), showed significant improvement in disease activity versus placebo in participants with Sjögren's disease, according to phase 3 clinical trial data.

Prof. Thomas Grader-Beck (Johns Hopkins University of Medicine, MA, USA) presented the results from the NEPTUNUS-1 (NCT05350072) and NEPTUNUS-2 (NCT05349214) global, randomised, placebo-controlled trials in participants with active Sjögren's disease [1]. The treatment consisted of subcutaneous ianalumab 300 mg monthly or placebo for 52 weeks in both trials, with an additional ianalumab 300 mg every 3 months arm in NEPTUNUS-2. Adults were eligible if they satisfied 2016 ACR/EULAR classification criteria, had a diagnosis ≤7.5 years prior, an EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥5, and a stimulated whole salivary flow rate of ≥0.05 mL/min. The primary endpoint was the change from baseline in ESSDAI at week 48. Overall, 275 and 504 participants were randomised in NEPTUNUS-1 and -2, respectively.

The primary endpoint was met in both trials, demonstrating the superiority of ianalumab over placebo. Ianalumab 300 mg monthly compared with placebo led to a mean difference in change from baseline in ESSDAI of -1.3 (95% CI -2.6 to 0.0; P=0.0496) in NEPTUNUS-1 and -1.0 (95% CI -2.0 to 0.0; P=0.041) in NEPTUNUS-2. Numerical improvements versus placebo were also observed with ianalumab 300 mg every 3 months, but they did not reach statistical significance.

Overall, infection rates were similar across treatment arms. One malignancy was reported with placebo and none with ianalumab in NEPTUNUS-1, while 4 malignancies were reported with ianalumab and none with placebo in NEPTUNUS-2.

"NEPTUNUS-1 and -2 are the first global, replicate, phase 3 studies in Sjögren's disease to meet their primary objective, showing a statistically significant improvement in ESSDAI," concluded Prof. Grader-Beck. He added that "ianalumab 300 mg monthly demonstrated a favourable safety profile, supporting a positive risk-benefit profile in Sjögren's disease."

1. Grader-Beck T, et al. Ianalumab demonstrates significant reduction in disease activity in patients with Sjögren's disease: Efficacy and safety results from two global Phase 3, randomized, placebo-controlled double-blind studies (NEPTUNUS-1 and NEPTUNUS-2). ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

CAR Treg cells show initial efficacy in hard-to-treat rheumatoid arthritis

SBT777101 is an autologous chimeric antigen receptor (CAR) regulatory T-cell (Treg) therapy specific for citrullinated proteins, designed to restore immunological tolerance in inflammatory diseases without exerting cytotoxic effects. Preliminary data with SBT777101 showed no dose-limiting toxicities and early signs of efficacy in patients with highly refractory rheumatoid arthritis.

Dr Minna Kohler (Massachusetts General Hospital, MA, USA) presented the findings from the ongoing Regulate-RA (NCT06201416), a first-in-humans, phase 1, open-label, dose-escalation trial of SBT777101 [1]. Participants were eligible if they had met the 2010 ACR/EULAR criteria for rheumatoid arthritis, had a Disease Activity Score 28 with C-reactive protein (DAS-28-CRP) >3.2, and had failed ≥3 disease-modifying antirheumatic drugs (DMARDs) with different mechanisms-of-action. Three participants were treated per dose level, with sequential dose escalation across 3 planned dose cohorts. The primary outcome was safety and tolerability, with efficacy assessed as an exploratory endpoint. The first 2 dose levels completed dose-limiting toxicity evaluation, and data were presented for 6 participants in total.

The most common adverse events were nausea, vomiting, and headache, occurring primarily in the first week after infusion. No cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or dose-limiting toxicities were observed. Overall, 4 of 6 participants achieved ≥50% reduction in swollen or tender joint counts at week 4 after infusion, with deeper and more durable responses in cohort 2 (the higher-dose group) from week 4 through week 24. In 1 responding participant, CAR Treg cells were detectable in a post-treatment synovial biopsy, providing preliminary evidence of target-tissue homing and persistence of the regulatory T-cell phenotype.

"In summary, Regulate-RA is an ongoing, dose-escalation phase 1 trial of SBT777101 autologous CAR Treg cells in participants with highly refractory rheumatoid arthritis," concluded Dr Kohler. "Interim safety and tolerability are favourable with no dose-limiting toxicities, and preliminary data indicate clinical signals of efficacy. Enrolment in cohort 3 is ongoing."

1. Kohler M, et al. A phase 1 study of autologous CAR-Treg cells in refractory rheumatoid arthritis: Interim report of safety and efficacy. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Telitacicept reveals positive efficacy data in Chinese patients with Sjögren's disease

Telitacicept, a recombinant fusion protein that simultaneously inhibits B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), showed significant improvements in disease activity scores versus placebo in patients with Sjögren's disease in China, with injection-site reactions reported as the most common adverse event.

Dr Dong Xu (Peking Union Medical College Hospital, China) presented results from a randomised, double-blind, placebo-controlled, phase 3 study (NCT05673993), conducted in multiple sites in China [1]. Patients were eligible if they were aged 18-70 years, met the 2016 ACR/EULAR classification criteria for Sjögren's disease, were anti-SSA (Ro) antibody-positive, and had an EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score ≥5. Randomisation was carried out to subcutaneous telitacicept 80 mg once weekly, 160 mg once weekly, or placebo for 48 weeks. Participants in the placebo group who had an inadequate response after week 24 were allowed to switch to telitacicept in a 1:1, blinded re-randomisation. The primary efficacy endpoint was the change from baseline in ESSDAI score at week 24. A total of 381 participants were enrolled.

Participants treated with telitacicept had greater reductions from baseline in ESSDAI scores at week 24 compared with placebo, corresponding to a least-squares mean difference versus placebo of -3.8 (95% CI -4.6 to -3.0; P<0.0001) for telitacicept 160 mg and -2.4 (95% CI -3.2 to -1.6; P<0.0001) for telitacicept 80 mg. Participants who switched from placebo to telitacicept after week 24 also showed clinical improvement; however, the difference compared with the continuous telitacicept groups remained significant through week 48.

The most commonly reported adverse events with telitacicept included injection-site reaction, upper respiratory tract infections, urinary tract infection, cough, and abnormal hepatic function.

The authors concluded that telitacicept met the study's primary efficacy endpoint. "Compared with placebo, both telitacicept 160 mg and 80 mg demonstrated consistent improvement in clinical symptoms through 48 weeks with a favourable safety profile. Greater improvements were observed in the telitacicept 160 mg group," said Dr Xu.

1. Xu D, et al. Efficacy and safety of telitacicept in patients with Sjögren's disease: Results from a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical study. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

From Mechanistic Insights to Real-World Practice

IDH1/2 mutations linked to inflammatory and rheumatological disorders

Somatic *IDH1/2* mutations, well known in haematological malignancies, have now been associated with rheumatological conditions and cytopenia, even in the absence of overt malignancy, according to a report by Dr Flore Castellan (New York University School of Medicine, NY, USA) [1].

Using data from 3 large biobanks, including the UK Biobank, All of Us, and a Mayo Clinic cohort of clonal cytopenia of uncertain significance (CCUS), researchers performed an unbiased mutation enrichment analysis in 265 UBA1-negative adults with VEXAS-like systemic autoinflammatory disease versus matched controls to identify novel genes involved in the development of systemic autoinflammatory disease.

Most participants had no haematological malignancy (72.8%), while 15.5% had myelodysplastic syndrome, 7.5% a myeloid neoplasm, and 4.2% a lymphoid neoplasm. Hotspot *IDH1/2* mutations were among the most frequent and biologically significant, detected in 5.7% of participants with VEXAS-like disease. Notably, about 25% of participants with *IDH1/2* mutations lacked any haematological malignancy and exhibited fewer co-mutations than those with haematological malignancy.

Across all 3 biobanks, *IDH1/2* mutations without concurrent haematological malignancy were significantly associated with rheumatologic conditions, elevated C-reactive protein (CRP) levels, and cytopenias.

"All in all, we observed that *IDH1/2* clonal haematopoiesis/CCUS co-occur with systemic inflammation with or without haematological malignancy," concluded Dr Castellan. "These mutations are associated with rheumatological conditions in large biobanks. We suggest that *IDH1/2* hotspot mutations are driving a treatable pre-malignant inflammatory condition, suggesting that screening for somatic *IDH1/2* mutations in patients with unexplained systemic inflammation could inform targeted treatment strategies."

1. Castellan F, et al. *IDH1/2* somatic hotspot mutations as independent drivers of autoinflammation. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

NTR-441 is an emerging treatment option for rheumatological conditions

NTR-441, a DNase1L3-albumin fusion protein, demonstrated acceptable safety in a phase 1 trial, with preliminary clinical efficacy observed in a patient with systemic lupus erythematosus (SLE) who had a deficiency in DNase1L3.

Dr Tobias Fuchs (Neutrolis Inc., MA, USA) reported the results from a first-in-humans study (NCT04941183) evaluating NTR-441 as a therapeutic approach to inactivate Neutrophil Extracellular Traps (NETs) [1]. The phase 1a part assessed single doses in healthy participants (n=35), followed by phase 1b, which involved single and multiple ascending doses in hospitalised participants with COVID-19 (n=16). Additionally, 1 participant with SLE and congenital DNase1L3 deficiency received NTR-441 at 3.0 mg/kg weekly for 3 months under compassionate use.

Pharmacodynamic analyses revealed that NTR-441 results in rapid and supraphysiological DNase1L3 levels shortly after infusion. NTR-441 was overall well tolerated, with most adverse events reported at the highest dose (10 mg). Infusion-related reactions were observed in 1 healthy volunteer and in the SLE participant, which were linked to the development of anti-drug antibodies.

In the lupus participant, clinical improvement across multiple organs was observed within 6 hours of the first administered dose, although partial recurrence of rash and episcleritis occurred before subsequent administrations. After 3 months, treatment was discontinued due to anti-drug antibodies, which affected clinical response. Notably, clinical improvement correlated with markers of NET degradation.

"These first-in-humans studies validate DNase1L3 analogues as a therapeutic strategy to inactivate NETs rapidly," concluded Dr Fuchs, "and the temporal association between NET clearance and clinical improvement implicates NETs as a key pathogenic driver."

A phase 2 trial is planned to evaluate NTR-441 in patients with anti-dsDNA-positive SLE and anti-citrullinated protein antibody-positive rheumatoid arthritis.

1. Reiff A, et al. Early evidence of proof-of-concept of an albumin-DNASE1L3 fusion protein (NTR-441) for the rapid enzymatic inactivation of NETs in SLE with DNASE1L3-deficiency. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Hydroxychloroquine blood level monitoring may reduce toxicity risk in lupus

Hydroxychloroquine (HCQ) blood levels ≥1,150 ng/mL are associated with an increased risk of treatment-related toxicity, suggesting this threshold could guide HCQ dose adjustments in patients with systemic lupus erythematosus (SLE).

Dr Shivani Garg (University of Wisconsin School of Medicine and Public Health, WI, USA) presented the data from a pooled analysis aimed at determining an upper therapeutic limit for HCQ monitoring in clinical practice. This analysis included 1,843 participants from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort (33 centres in 11 countries across North America, Europe, and Asia), the Wisconsin Lupus Cohort Registry, and 3 French studies. Participants were eligible for inclusion in the analysis if they had baseline whole-blood and serum HCQ measurements, and the outcomes included HCQ-related toxicity.

Statistical analysis demonstrated that HCQ concentrations above 1,150 ng/mL did not improve clinical efficacy but were associated with a higher risk of toxicity. Multivariable regression analysis showed both age (per 10-year increase) and cumulative HCQ dose (per 1,000 g increase) significantly predicted HCQ toxicity, whereas other factors, including sex, race, and eGFR status, were not associated with increased odds of developing toxicity. Participants with HCQ blood levels of ≥1,150 ng/mL had a 2-fold higher risk of developing toxicity (adjusted OR 2.09; 95% CI 1.22-3.67; P=0.01).

Subgroup analysis by chronic kidney disease stage revealed that stages 3 and 4 were associated with approximately double the odds of exceeding the 1,150 ng/mL HCQ blood level threshold, even with weight-adjusted dosing.

"Safe and effective HCQ concentrations likely lie between 750-1,150 ng/mL," concluded Dr Garg. "These findings support the role of therapeutic HCQ blood level monitoring to optimise efficacy and minimise toxicity, particularly in patients with chronic kidney disease stage 3 or higher."

1. Garg S, et al. Defining safe hydroxychloroquine blood levels: Time to switch to precision monitoring for optimized lupus care. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Many high-risk post-menopausal women in the USA remain undertreated for osteoporosis

A large proportion of post-menopausal women in the USA who are at very high risk of fracture are either undertreated or receive oral bisphosphonates instead of other guideline-recommended therapies.

Dr Xiaodong Li (Amgen Inc., CA, USA) presented the results from a retrospective cohort study using Optum® Market Clarity Bone Data [1]. Eligible participants were post-menopausal women aged ≥55 years with a diagnosis of osteoporosis, or a history of fracture, or osteoporosis medication use, with at least 455 days of continuous database enrolment, and no history of Paget's disease or metastatic cancer.

Two cohorts were defined:
- a treated cohort (initiated treatment between April 2019 and the end of September 2023), and
- an untreated cohort (no therapy initiation in the 15 months preceding January 2023).

Fracture risk status was classified using the American Association of Clinical Endocrinology (AACE) criteria.

Among the 41,597 treated participants, 56.3% received an oral bisphosphonate. Within this group, 12.6% had a recent fracture (≤12 months), of whom 41.5% were treated with an oral bisphosphonate. Among those without a fracture history but with a T-score ≤-3 (0.8%), 36.8% received an oral bisphosphonate, while among those with a very high-risk Fracture Risk Assessment Tool (FRAX) score (38.2%), 55.6% were receiving oral bisphosphonates. Overall, 51.7% of all very high-risk participants in the treated cohort (n=21,466) were receiving oral bisphosphonates. In the untreated cohort (n=318,140), 37.1% (n=118,065) met the criteria for a very high risk of fracture but were not receiving therapy.

"Among treated post-menopausal women with osteoporosis at very high fracture risk, more than half received oral bisphosphonates, which does not align with current guidelines recommendations for initial therapy," concluded Dr Xiaodong. "Over 1/3 of untreated women with osteoporosis are at very high risk of fracture and are eligible for treatment with osteoanabolic therapies, denosumab, or zoledronic acid according to current guidelines."

1. Chien HC, et al. Distribution of fracture risk status and osteoporosis treatment use among post-menopausal women with osteoporosis in the United States. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.

Head-to-head trial shows secukinumab superior to ustekinumab in psoriatic arthritis

In a head-to-head comparison, secukinumab, a human monoclonal antibody targeting interleukin-17 (IL-17), demonstrated better disease control and fewer treatment discontinuations than ustekinumab in patients with psoriatic arthritis (PsA) who had previously received tumour necrosis factor-alpha (TNFα) inhibition.

The AgAIN trial (NCT04632927) was a randomised, double-blind, active-controlled, multicentre trial assessing secukinumab versus ustekinumab across 28 centres in Germany. Prof. Frank Behrens (Fraunhofer Institute for Translational Medicine and Pharmacology, Germany) presented the results [1]. Eligible participants were included if they had met the Classification Criteria for Psoriatic Arthritis (CASPAR) for ≥6 months before randomisation, had ≥3 tender joints and ≥3 swollen joints, inadequate response or intolerance to ≥1 TNFα inhibitor and to conventional disease-modifying antirheumatic drugs (cDMARDs), and active or history of psoriasis. Participants were randomised 1:1 to receive secukinumab 300 mg (weekly for 4 weeks, then every 4 weeks thereafter up to week 24), or ustekinumab 45 or 90 mg (weeks 4, 8 and 16). Efficacy was assessed at week 28 using the Health Assessment Questionnaire-Disability Index (HAQ-DI) tool. In total, 119 participants were randomised.

HAQ-DI scores increased continuously over time in both groups, but the response rate at week 28 was higher with secukinumab than with ustekinumab (57.1% vs 27.0%). Among participants with concurrent active psoriasis, more achieved a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) (60.7% vs 46.0%) and PASI-90 (48.2% vs 39.7%) responses with secukinumab compared with ustekinumab. Both therapies had expected safety profiles, but treatment discontinuations due to adverse events were less frequent with secukinumab (3.6% vs 12.7%).

Overall, this head-to-head trial demonstrated that secukinumab provides superior disease control and tolerability compared with ustekinumab in patients with PsA who have been previously exposed to TNFα inhibitors and cDMARDs.

1. Behrens F, et al. AgAIN Study: First head-to-head trial of secukinumab vs. ustekinumab in TNFα inhibitor-experienced psoriatic arthritis patients reveals better efficacy across multiple domains. ACR Convergence, 24–29 October 2025, Chicago, IL, USA.