Results: No differences were seen on comparing the baseline parameters of the 3 groups. In comparison to the baseline, there was significant increase in the BMD in the 3 groups, Denosumab/Zol/Aln at both spine and hip ($P = 0.02$) at 5-, 3- and 5-years of treatment respectively. In the denosumab group, at 5-years of therapy, there was significant decrease in falls risk score (-1.4 , 95% CI = -2.8 to -0.7 ; $P = .01$), significant improvements in the grip strength ($+4.2$ Kg, $P = 0.01$), SPPB score (1.2 points; 95% CI = -0.07 to 2.2 ; $P = .02$), TUG (1.7 seconds; 95% CI = -2.2 to 0.1 ; $P = .031$) and gait speed (0.1 m/s; 95% CI = 0.03 - 0.2 ; $P = .01$). Zol and Aln improved significantly SPPB score (0.9 and 0.8 points; $P = .04$), TUG (1.4 and 1.3 seconds; $P = .05$) and gait speed (0.2 and 0.3 m/s; $P = .02$) respectively, however, there was no significant change in the falls risk ($p = 0.06$ and 0.07 respectively). 1-year after stopping Denosumab, there was significant worsening of the falls risk score, grip strength, SPPB score, TUG and gait speed ($P = 0.1$). There was no difference in all the measures 1-year after stopping Zol and Aln. There was no relation to the increase in BMD gained.

Conclusion: Denosumab displayed positive impact and significant improvements in physical performance, grip strength and gait speed. Also, Denosumab, enhanced multidirectional agility as depicted by TUG. Collectively, this would explain the reduction of falls risk which got worse on stopping the medication.

Osteoporosis and sarcopenia share similar risk factors, highlighting muscle-bone interactions, which may result in debilitating consequences, such as falls and fractures. RANK/RANKL/OPG pathway, a key regulator of bone homeostasis, may contribute also to the regulation of skeletal muscle integrity and function.

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Clinical symposium axSpA: Treat-to-target in axSpA: myth or reality?

OP0314

FACTORS ASSOCIATED WITH 5-YEAR DRUG-FREE REMISSION IN EARLY ONSET AXIAL SPONDYLOARTHRITIS PATIENTS: DATA FROM DESIR COHORT

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Background: It is recommended to target remission when treating a patient with a chronic inflammatory rheumatism. To date, drug-free (DF) remission has been poorly investigated in axial Spondyloarthritis (axSpA).

Objectives: 1/To estimate the frequency of patients in DF remission after 5 years of follow-up in a cohort of early axSpA and 2/to assess the factors associated with 5-year DF Remission.

Methods: *Patients:* All patients included in DESIR (DEvenir des Spondyloarthrites Indifférenciées Récentes) cohort were selected for this analysis. *Definition of 5-year DF Remission:* 1/all patients in ASAS partial remission and/or ASDAS<1.3 at 5 year visit and 2/ taking no disease modifying anti-rheumatic drugs (DMARDs, including synthetic and biologics) only at 5-year visit (patients could have received DMARD before the 5-year visit) and 3/ with a NSAIDs score ≤ 25 at the 5-year visit. *Covariates analysed:* age, gender, smoking status, body mass index, disease classification criteria (ASAS, Amor, ESSG, New York), presentation at onset (peripheral or extra-articular features), disease activity at onset (BASDAI, ASDAS-CRP, CRP, MASES, TJC or SJC), functional impairment at baseline (BASFI, HAQ-AS, BASMI), comorbidities, baseline imaging data (radiographic sacroiliitis, mSASSS, MRI sacroiliitis, spine MRI Berlin score), NSAID intake within 6 months before baseline visit and 5-year treatment intake (including DMARDs, corticoids and NSAIDs). *Statistical analysis:* The associations between each of these clinical factors and the 5-year DF remission were tested by logistic regression. A multivariate model was built, stepwise procedure, to identify the independent variables associated with 5-year DF remission.

Results: Of the 708 patients included in DESIR cohort, 419 were seen at the 5-year visit and 72 (17.0%) were in DF remission (50% of males, aged of 33.08 years (SD:8.0), disease duration: 1.26 years (SD: 0.72), HLA-B27 in 71%, 26.4% had a MRI sacroiliitis). Patients in 5-year DF remission had lower symptom duration (1.3 year versus 1.6 year, $p=0.01$) had lower disease activity (BASDAI at baseline: 30.1 versus 46.1, $p<0.0001$, ASDAS-CRP: 1.96 versus 2.75, $p<0.0001$,

CRP: 3.9 versus 8.6, $p=0.01$) had less peripheral involvement (at least 1 enthesitis at baseline: $n=33$ (45.8%) versus $n=226$ (65.1%), $p=0.002$; at least 1 painful joint at baseline: $n=24$ (33.3%) versus $n=196$ (56.5%), $p=0.0006$) less functional impairment (HAQ-AS: 0.32 versus 0.69, $p<0.0001$, BASFI: 14.3 versus 32.1, $p<0.0001$, BASMI: 1.98 versus 2.51, $p<0.0001$), and had lower NSAIDs intake at baseline (NSAIDs score: 28.2 versus 48.1, $p=0.0001$). Interestingly, there was no difference in sacroiliac bone marrow oedema on MRI while Berlin scores on spine MRI were lower in patients in 5-year DF remission (Berlin score mean: 0.41 versus 1.24, $p=0.03$). During the 5 years of follow-up, patients in 5-year DF remission received less often analgesics ($n=46$ (63.9%) versus $n=297$ (85.3%), $p<0.0001$) and anti-TNF ($n=1$ (1.4%) versus $n=182$ (52.5%), $p<0.0001$), but there was no difference in NSAID or csDMARD intake between groups until the 4-year visit. After multivariate analysis, the variables that remained associated with 5-year DF remission were lower symptom duration (OR[95%CI]=0.58[0.36-0.88], $p=0.01$), lower baseline ASDAS-CRP (OR[95%CI]=0.50[0.32-0.76], $p=0.002$) or NSAIDs score (OR[95%CI]=0.54[0.34-0.81], $p=0.004$) and not initiating an anti-TNF during the 5 years of follow-up (OR[95%CI]=0.029[0.00-0.14], $p=0.0005$).

Conclusion: DF remission is rare, 5 years after onset of axSpA. Patients with longer symptom duration, higher baseline ASDAS-CRP and NSAIDs scores were less often in DF remission, while imaging and biological data did not predict DF remission.

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OP0315

WHICH RESPONSE OR STATUS CRITERION DISCRIMINATES BEST IN AXSPA?

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Background: Response criteria and disease activity status used to assess treatment efficacy in axial spondyloarthritis (axSpA) are: the ASAS response criteria (ASAS20; 40; 5/6 and partial remission - PR), BASDAI50 and ASDAS-based criteria (clinically important/major improvement -CII/MI; low disease activity/inactive disease -LDA/ID). These outcomes are variably used in RCTs testing biological (b) and targeted-synthetic (ts)DMARDs. However, it remains unknown which are the most discriminative.

Objectives: To compare the ability of different criteria to discriminate between the response to active treatment and placebo in axSpA.

Methods: A systematic literature review was performed in Medline and Embase to identify RCTs of b- and tsDMARDs. Placebo-controlled RCTs meeting the primary endpoint were included provided they reported ≥ 2 response/status criteria. Outcomes were collected at the timepoint of primary endpoint assessment (PEA). Risk of bias was evaluated by The Cochrane tool. Meta-analysis with the Mantel-Haenszel method was conducted to calculate the Chi-square (χ^2) between percentages of patients fulfilling each criterion in the treatment arm versus the placebo arm (higher χ^2 , better discrimination). Comparisons among criteria were conducted evaluating their performances across RCTs reporting the exact same outcomes at the PEA. Different sets of RCTs were used for the comparisons depending on the available outcomes (Table).

Results: 29 RCTs fulfilled inclusion criteria. In total, 23/29 RCTs with PEA at 12, 14 or 16 weeks, all at a low risk of bias, could be considered for meta-analysis. Other 6 RCTs had later (e.g 24 weeks) or earlier (e.g. 6 weeks) PEA. Out of the 23 RCTs, only 16 reported at least a minimum set of ASAS20, -40, -PR and BASDAI50 (Table, Set 1): discriminative performances for ASAS40 were >ASAS20>BASDAI50>ASAS-PR. In 11/16 RCTs ASAS5/6 was also included (Table, Set 2): this criterion showed the best performances among ASAS-based response criteria. 8/16 RCTs additionally included some ASDAS-based criteria (Table, Set 3): ASDAS-CII and -MI showed a much higher discrimination compared to the ASAS-based criteria. In only 3 trials could all criteria be compared, with the ASDAS-CII and -MI appearing as the most discriminative criteria, followed by ASAS 5/6 (Table, Set 4).

Conclusion: Response criteria are more discriminative than status criteria. ASDAS-CII and ASDAS-MI showed the best discrimination between treatment/placebo arms. Using the ASDAS-CII as primary outcome in future RCTs can reduce the number of patients needed to be included while keeping the same statistical power.

Table. Discriminative performances of response and status criteria in RCTs of biological and targeted synthetic DMARDs in axial spondyloarthritis

Minimum set of outcomes	Set 1: ASAS20,- 40,-PR, BASDAI50	Set 2: ASAS20,-40,- 5/6,-PR BASDAI50	Set 3: ASAS20,-40,- 5/6,-PR BASDAI50 ASDAS-CII, -MI, -ID	Set 4: All
N° of RCTs Total=16*	16	11	8	3
Descending X ² order	X ²	X ²	X ²	X ²
1	ASAS40 339	ASAS5/6 334	ASDAS-CII 309	ASDAS-CII 124
2	ASAS20 316	ASAS40 266	ASDAS-MI 253	ASDAS-MI 65
3	BASDAI50 297	ASAS20 254	ASAS40 169	ASAS5/6 48
4	ASAS-PR 146	BASDAI50 248	BASDAI50 163	BASDAI50 39
5	-	ASAS-PR 119	ASDAS-ID 117	ASAS40 34
6	-	-	ASAS20 98	ASDAS-LDA 27
7	-	-	ASAS-PR 80	ASAS-PR 22
8	-	-	-	ASAS20 21
9	-	-	-	ASDAS-ID 7

Legend. *total of 16 RCTs analysed, with different sets of RCTs within the 16 analysed based on the availability of response criteria; X²=Chi-square; RCTs=randomized controlled trials; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; ASAS= Assessment in SpondyloArthritis International Society; PR= partial remission; CII= clinically important improvement; MI= major improvement; LDA= low disease activity; ID= inactive disease

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New perspectives on therapeutic immune tolerance.

OP0316 EMERGING BEST-IN-CLASS IL-2 VARIANT HIGHLIGHTS TREG-DIRECTED THERAPY FOR AUTOIMMUNE DISEASE

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Background: Impairment or deficiency of regulatory T cells (Treg) is associated with chronic inflammation and autoimmune diseases. Interleukin 2 (IL-2) is a cytokine indispensable for Treg expansion and immunosuppressive function. However, expansion of cytotoxic effector T (Teff) and NK cells and the associated vascular leakage side effect limit the use of IL-2 in autoimmune diseases [1].

Objectives: Cugene developed a long-acting IL-2 variant with high Treg specificity and low toxicity to restore immune homeostasis and self-tolerance, and potentially cure autoimmune and inflammatory diseases.

Methods: IL-2 variants were generated based on the quaternary structure of IL-2 and IL-2Rαβ (alpha, beta, gamma) complex. Biological activity was determined by examining differential signaling activity in induction of STAT5 phosphorylation in defined lymphocyte populations of human PBMC using flow cytometry. Binding activity was evaluated by ELISA. Pharmacokinetics, pharmacodynamics, safety and tolerability were assessed in mice and cynomolgus monkeys. Treg suppressive function was determined *in vivo/ex vivo*, and anti-inflammatory and anti-antibody production efficacy were determined in delayed-type hypersensitivity (DTH) and T-cell-dependent antibody response (TDAR) models.

Results: Structure-based rational design and activity-guided fine-tuning generated an optimized IL-2 variant, CUG252. It demonstrated a strong and near wild-type IL-2 ability to stimulate STAT5 phosphorylation in IL-2Rαβ dominant Treg cells but abolished activities in IL-2Rβγ dominant effector CD4, CD8 and NK cells. This was a result of biased binding activity to IL-2Rα while dramatically

attenuated binding to IL-2Rβγ complex. In mice and monkeys, administration of CUG252 resulted in dose-dependent increases in Treg proliferation and expansion by more than 10- and 30-fold, respectively, with largely abolished activities in CD4+ T conventional, cytotoxic CD8+ Teff and NK cells. The ratio of Treg/Teff cells achieved was as high as 0.4 in mice and 1.2 in monkeys. Both CD4+ and CD8+ Tregs were expanded with preferential increases in memory over naïve subsets. A substantial increase in Treg-suppressive capacity over T effector cells was corroborated by enhanced expression of functional and inhibitory markers, including CD25, Foxp3, PD-1, CTLA-4, Tim3 and ICOS. In DTH and TDAR models, CUG252 strongly inhibited antigen-driven inflammation, B cell maturation, and antibody production. The sustained PK/PD profile supports monthly dosing or better in humans. CUG252 was well-tolerated and no changes in body weight, body temperature, clinical pathology or signs of vascular leakage were observed. Moreover, CUG252 demonstrated superior manufacturability.

Conclusion: CUG252 demonstrates an emerging best-in-class profile among IL-2 variants. It displayed exquisite Treg-selectivity while retaining potency comparable to wild-type IL-2. It showed strong anti-inflammatory and anti-antibody production efficacy with significantly improved therapeutic index and manufacturability. Its favorable drug-like property and robust preclinical efficacy warrant further evaluation in patients with a variety of inflammation and autoimmune diseases.

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Pathological calcification in rheumatic diseases

OP0317 ACCURACY OF THE OMERACT DEFINITIONS FOR IDENTIFICATION OF CALCIUM PYROPHOSPHATE CRYSTALS WITH ULTRASOUND: FINAL RESULTS OF THE OMERACT US IN CPPD SUB-TASK FORCE STUDY

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Background: The OMERACT Ultrasound (US) in calcium pyrophosphate deposition disease (CPPD) sub-task force has been working on the use of US in CPPD since 2014 first creating definitions for CPPD identification and then assessing the reliability[1].

Objectives: Objective of this study is to assess the diagnostic accuracy (truth) of US in CPPD.

Methods: Consecutive patients waiting to undergo knee replacement surgery due to osteoarthritis were enrolled in 12 centres from 6 countries. Each patient underwent US examination of the knee, focusing on the menisci and the hyaline cartilage, the day prior to surgery, scoring each site for presence/absence of CPP as defined previously[1]. After surgery, the menisci and the condyles were retrieved and examined microscopically. Six samples were collected, both from the surface and from the internal part of menisci and cartilage trying to cover a large part of it. All slides were observed under transmitted light microscopy and by compensated polarised microscopy. A dichotomous score was given for the presence/absence of CPP. US and microscopic analysis were performed by different operators, blind to each other's findings.