

in patients with PMR. Glucocorticoid treatment remains the mainstay treatment for PMR. A study published in 1996 reported that macrophages dominate the inflammatory infiltrates in the glenohumeral synovium of PMR patients¹, suggesting the importance of these cells in the immunopathology of PMR. However, the functional and phenotypical heterogeneity of the tissue-infiltrating macrophages in PMR remains obscure. Although treatment with anti-IL-6 receptor (tocilizumab) has shown promising results², it is unclear whether macrophages contribute to IL-6 production in PMR. Additionally, anti-GM-CSF receptor therapy (mavrilimumab), recently shown to be efficacious in the closely related disease giant cell arteritis³, may also be useful for the treatment of PMR. Knowledge on the functional heterogeneity of monocytes/macrophages in PMR may aid in identifying novel therapeutic targets for this condition.

Objectives: To determine the phenotype of monocyte/macrophages in peripheral blood, bursal/tenosynovial fluid and bursal tissue of patients with PMR.

Methods: Paired peripheral blood (PB), bursal/tenosynovial fluid (SF) and bursal tissue biopsy samples from 11 PMR patients were included in our study. Bursal and tenosynovial samples were obtained from the shoulder. Distribution of the monocyte subsets (classical, intermediate and non-classical monocytes) was determined based on the level of CD14 and CD16 expression by flow cytometry. To study monocyte activation status, markers of 'M1' like (CD80 and CD64) and 'M2' like (CD206 and FR β) macrophage polarization were included in the flow cytometry analysis. Immunohistochemistry of bursal tissue biopsies was focused on macrophage markers (CD68, CD86, CD64, CD206 and FR β) and proinflammatory cytokines (IL-6 and GM-CSF), which were scored semi-quantitatively. Double immunofluorescence stainings were performed to determine the expression of IL-6 and GM-CSF by tissue-infiltrating macrophages in bursal tissue.

Results: Monocytes were detected in the SF of PMR patients. The proportion of classical monocytes was significantly lowered ($p=0.001$) in SF versus PB, while the proportion of intermediate monocytes was significantly elevated ($p=0.001$). The expression of CD206 was significantly elevated ($p=0.001$) but not FR β in SF monocytes, suggesting GM-CSF skewed phenotype. In bursal tissue, macrophages displayed mixed 'M1'/M2' traits with high expression of all macrophage polarization markers. Proinflammatory cytokines IL-6 and GM-CSF were highly expressed throughout the bursal tissue biopsies. Double immunofluorescence staining confirmed the expression of IL-6 and GM-CSF by the infiltrating macrophages.

Conclusion: SF monocytes and bursal tissue macrophages show a pro-inflammatory phenotype in PMR. Moreover, tissue-infiltrating macrophages show a prominent IL-6 and GM-CSF response in PMR. Our data add to the rationale of targeting IL-6 and GM-CSF as treatment options in PMR.

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Acknowledgements: This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology. The PMR Research On disease Mechanisms In Synovium (PROMIS) study was also funded by the Rheumatology Grant (Dutch Society for Rheumatology) and Mandema Stipend (University Medical Center Groningen).

Disclosure of Interests: William Feby Jiemy: None declared, Rosanne Reitsema: None declared, Anqi Zhang: None declared, Maria Sandovici: None declared, Annemieke Boots: None declared, Peter Heeringa: None declared, Elisabeth Brouwer Speakers bureau: E. Brouwer reports speaker and consulting fees from Roche in 2017-2018, outside the submitted work, Consultant of: E. Brouwer reports speaker and consulting fees from Roche in 2017-2018, outside the submitted work, Kornelis van der Geest Consultant of: K. van der Geest reports personal fees from Roche, outside the submitted work.

DOI: 10.1136/annrheumdis-2022-eular.4396

AxSpA drug treatment: new and old drugs

OP0016

EFFICACY AND SAFETY OF UPADACITINIB IN PATIENTS WITH ACTIVE NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 TRIAL

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Background: Janus kinase (JAK) inhibitors have been recognized as a potential therapeutic option in ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis (r-axSpA).¹ Upadacitinib (UPA), a JAK inhibitor, has demonstrated efficacy and safety in the treatment of AS²; however, no JAK inhibitor studies have been conducted in non-radiographic axSpA (nr-axSpA) to date.

Objectives: To assess the efficacy and safety of UPA in patients (pts) with active nr-axSpA.

Methods: SELECT-AXIS 2 (NCT04169373) was conducted under a master protocol comprising two independent studies, one in an AS population with an inadequate response to biologic disease-modifying antirheumatic drugs and one in an nr-axSpA population. The nr-axSpA study is a randomized, double-blind, placebo(PBO)-controlled, phase 3 trial that enrolled adults ≥ 18 years with a clinical diagnosis of nr-axSpA (who also fulfilled 2009 ASAS classification criteria for axSpA but did not meet the radiologic criterion of modified New York criteria), who had objective signs of active inflammation consistent with axSpA on MRI of the sacroiliac (SI) joints and/or high sensitivity C-reactive protein (hs-CRP) >upper limit of normal (2.87 mg/L) at screening, and who had BASDAI and pt's assessment of total back pain scores ≥ 4 based on a 0 to 10 numeric rating scale at study entry. Pts were randomized 1:1 to receive oral UPA 15mg once daily (QD) or PBO during a 52-week (wk) double-blind treatment period. The primary endpoint was ASAS40 response at wk 14. Multiplicity-controlled secondary endpoints assessed at wk 14 included BASDAI50, ASDAS ID (<1.3), ASDAS LDA (<2.1), ASDAS PR, and ASAS20, and the change from baseline (Δ) in ASDAS (CRP), SPARCC MRI SI joint inflammation score, total and nocturnal back pain, BASFI, ASQoL, ASAS HI, BASMI, and MASES. Treatment-emergent adverse events (TEAEs) are reported through wk 14 for pts who received ≥ 1 dose of study drug.

Results: Of 314 pts randomized at baseline, 313 received study drug (UPA 15mg, n=156; PBO, n=157) and 295 (94%) received study drug through wk 14. Baseline demographic and disease characteristics were balanced across treatment groups and consistent with an active nr-axSpA population (58% female; mean age 42.1 years; mean BASDAI 6.9; mean hs-CRP 12.1 mg/L).

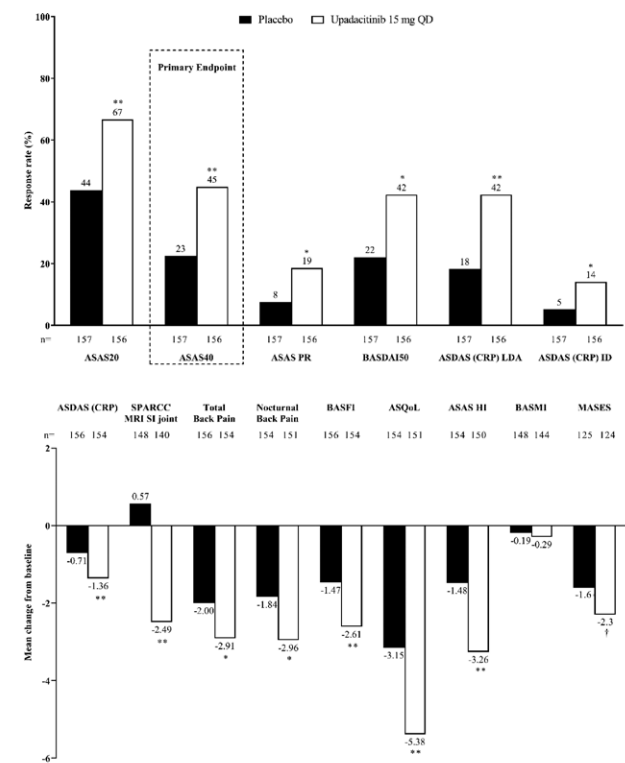


Figure. Analysis of Primary and Multiplicity-Controlled Secondary Endpoints at Wk 14

ASAS20=Assessment of SpondyloArthritis International Society 20 response; ASAS40=Assessment of SpondyloArthritis International Society 40 response; ASAS HI=Assessment of SpondyloArthritis International Society Health Index; ASAS PR=Assessment of SpondyloArthritis International Society partial remission; ASDAS (CRP)=Ankylosing Spondylitis Disease Activity Score-C-reactive protein; ASDAS (CRP) ID=Ankylosing Spondylitis Disease Activity Score-C-reactive protein low disease activity; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI50=at least 50% improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CMH=Cochran-Mantel-Haenszel; MASES=Massachusetts Ankylosing Spondylitis Enthesis Score; MMRM=mixed effect model for repeated measurements; NRI-MI=non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; QD=once daily; SPARCC=Spondyloarthritis Research Consortium of Canada. *Nominal $P < 0.05$. ** $P < 0.0001$. Significant in multiplicity-adjusted analysis. ASDAS LDA was defined as ASDAS (CRP) < 2.1 and ASDAS ID as ASDAS (CRP) < 1.3 . MASES was assessed in pts with baseline enthesitis. Binary endpoints were analyzed using the CMH test, and NRI-MI was used to handle missing data. Continuous endpoints were analyzed using MMRM. N was the number of unique subjects contributing to MMRM model estimates.

A significantly higher ASAS40 response rate at wk 14 was achieved with UPA vs PBO (45% vs 23%; $P < 0.0001$; Figure 1). Statistical significance was also achieved in the first 12 of the 14 multiplicity-controlled secondary endpoints (ie, all endpoints except BASMI and MASES) at wk 14 for UPA compared with PBO ($P < 0.01$; Figure 1). The proportion of pts who experienced a TEAE was similar between treatment groups (UPA, 48%; PBO, 46%). Serious TEAEs and TEAEs leading to discontinuation were reported in 4 (2.6%) pts treated with UPA and 2 (1.3%) pts treated with PBO, respectively. Few pts had serious infection or herpes zoster (each 2 [1.3%] pts on UPA; each 1 [0.6%] pt on PBO, respectively). Uveitis was reported in 1 (0.6%) pt on UPA who had a history of uveitis and none on PBO. No malignancy other than non-melanoma skin cancer, major adverse cardiovascular events, venous thromboembolic events, inflammatory bowel disease (IBD), or death were reported in the study; 1 event of basal cell carcinoma occurred with PBO.

Conclusion: UPA 15 mg QD demonstrated significantly greater improvements in disease activity, pain, function, quality of life, and MRI-detected SI joint inflammation than PBO after 14 wks of treatment in pts with active nr-axSpA. The safety profile of UPA was consistent with what has been observed with other inflammatory musculoskeletal diseases,³⁻⁵ and no new risks were identified. These results support the potential use of UPA in pts with active nr-axSpA.

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Acknowledgements: AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, review, and approval of the abstract. No honoraria or payments were made for authorship. Medical writing support was provided by Julia Zolotarjova, MSc, MWC, of AbbVie.

Disclosure of Interests: Atul Deodhar Consultant of: AbbVie, Amgen, Aurinia, BMS, Celgene, GSK, Janssen, Lilly, MoonLake, Novartis, Pfizer, and UCB, Grant/research support from: AbbVie, GSK, Lilly, Novartis, Pfizer, and UCB, Filip van den Bosch Speakers bureau: AbbVie, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, Consultant of: AbbVie, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, Denis Poddubnyy Speakers bureau: AbbVie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, and UCB, Consultant of: AbbVie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, and UCB, Grant/research support from: AbbVie, MSD, Novartis, and Pfizer, Walter P Maksymowych Consultant of: AbbVie, Boehringer Ingelheim, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB, Grant/research support from: AbbVie, Novartis, and Pfizer, Désirée van der Heijde Consultant of: AbbVie, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, GSK, Janssen, Lilly, Novartis, Pfizer, UCB, Employee of: Director of Imaging Rheumatology BV, Tae-Hwan Kim Speakers bureau: AbbVie, Celltrion, Kirin, Lilly, and Novartis, Mitsumasa Kishimoto Consultant of: AbbVie, Amgen, Astellas BioPharma, Asahi-Kasei Pharma, Astellas, Ayumid Pharma, BMS, Chugai, Daiichi Sankyo, Eisai, Gilead, Janssen, Kyowa Kirin, Lilly, Novartis, Ono Pharma, Pfizer, Tanabe-Mitsubishi, Teijin Pharma, and UCB, Yuanyuan Duan Shareholder of: May own AbbVie stock or options, Employee of: AbbVie, Yihan Li Shareholder of: May own AbbVie stock or options, Employee of: AbbVie, Aileen Pangan Shareholder of: May own AbbVie stock or options, Employee of: AbbVie, Peter Wung Shareholder of: May own AbbVie stock or options, Employee of: AbbVie, In-Ho Song Shareholder of: May own AbbVie stock or options, Employee of: AbbVie.

DOI: 10.1136/annrheumdis-2022-eular.2534

OP0017

RECAPTURE RATES WITH IXEKIZUMAB AFTER WITHDRAWAL OF THERAPY IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS: RESULTS AT WEEK 104 FROM A RANDOMIZED PLACEBO-CONTROLLED WITHDRAWAL STUDY

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Background: COAST-Y is the first study to evaluate the effect of continuing vs withdrawing an IL-17A antagonist, ixekizumab (IXE) on the maintenance of disease control in patients (pts) with ankylosing spondylitis and non-radiographic axial spondyloarthritis through 104 Weeks (wks).

Objectives: Here, we describe the final results of pts re-randomized to either placebo (PBO; IXE Withdrawal) or IXE, who experienced flare, and recaptured response before or after open label retreatment during COAST-Y.

Methods: COAST-Y (NCT03129100) is a Phase 3, long-term extension study that included a double-blind, PBO-controlled, randomized withdrawal-retreatment period (RWP). Eligible pts who completed an originating study (COAST-V, -W, or -X) entered a 24-Week (Wk) lead-in period and received 80 mg IXE every 2 (Q2W) or 4 wks (Q4W) (the treatment regimen at the end of the originating study); pts receiving PBO at the end of COAST-X were assigned to IXE Q4W in COAST-Y. Pts who achieved remission (Ankylosing Spondylitis Disease Activity Score (ASDAS) <1.3 (inactive disease; ID) at least once at Wk 16 or 20, and <2.1 (low disease activity; LDA) at both visits) were randomized 2:1 at Wk 24 to continue IXE (as per lead-in period) or withdrawn to PBO. Pts who subsequently experienced flare (ASDAS ≥ 2.1 at 2 consecutive visits or ASDAS >3.5 at any visit) were switched to open label IXE Q2W or Q4W at the next visit (same as lead-in period). Time to first flare was analyzed using the Kaplan-Meier method with treatment comparison performed using log-rank test. The observed proportion of pts who recaptured ASDAS LDA and ID were summarized for pts who experienced flare and were retreated with open label IXE.

Results: A total of 155 pts met the criteria for remission and entered the RWP (PBO [IXE withdrawal], N=53; IXE Q4W, N=48; IXE Q2W, N=54) and 138 completed Wk 104. At Wk 104, significantly more pts in the combined IXE group (75.5%, $p < 0.001$, IXE Q4W: 75.0%, $p < 0.001$; IXE Q2W: 75.9%, $p < 0.001$) remained flare free through Wk 104 vs PBO (Figure 1). Notably, 35.8% of pts on PBO (IXE withdrawal) never experienced flare. Of the PBO pts who experienced flare and were retreated during Wk 24-104 (N=28), 4 recaptured LDA before switching to open label IXE retreatment, while 23 recaptured LDA and 19 met ID after switching (Table 1). Of the continuously treated IXE pts (N=13), 7 recaptured LDA before switching to open label IXE retreatment, while 5 recaptured LDA and 4 met ID after.

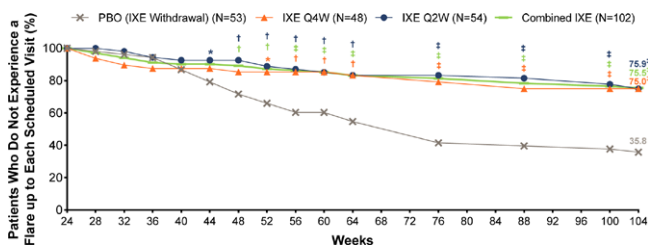


Figure 1. The proportion (%) of patients who remained flare free through 104 weeks. $^{\ddagger}p < 0.001$, $^{\dagger}p < 0.01$, $^*p < 0.05$ vs PBO (IXE Withdrawal).

Table 1. Recapture of first treatment response before or after switching to open label IXE through 104 weeks among placebo (ixekizumab withdrawal)-treated patients who experienced a flare and retreated

Total patients who flared and were switched to open-label ixekizumab retreatment	Placebo (ixekizumab withdrawal) (N=28)	
ASDAS disease activity status	LDA	ID
Recaptured response before open label ixekizumab retreatment	4	1
Recaptured response with open label ixekizumab retreatment (≤ 16 weeks)	23	14
Recaptured response with open label ixekizumab retreatment (> 16 weeks)	0	5
Total patients who recaptured response at week 104	27/28 (96%)	20/28 (71%)

Data are presented as n, (%) for the total row and n only for all other rows. In each column, the denominator is 28. ASDAS, Ankylosing Spondylitis Disease Activity Score; ID, inactive disease; LDA, low disease activity including ID; N, number of patients in the analysis population.

Conclusion: Pts continuously treated with IXE were less likely to experience flare vs pts on PBO (IXE withdrawal). The vast majority of pts withdrawn from IXE to PBO recaptured at least LDA and over half met ID with IXE retreatment. This may provide support for pts who require interruption in therapy.

Acknowledgements: This study was sponsored by Eli Lilly and Company. Medical writing services were provided by Ediel Hughes, PhD and Sumeet Sood, PhD of Eli Lilly and Company, and was funded by Eli Lilly and Company.

Disclosure of Interests: Robert B.M. Landewé Consultant of: Rheumatology Consultancy BV, AbbVie, UCB, Pfizer, Eli Lilly and Company, Novartis, and Celgene, Denis Poddubnyy Speakers bureau: AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and UCB Pharma, Consultant of: AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and UCB