co-expression was quantified. CD206 immunofluorescence of skin biopsies was also performed.
Macrophages were co-cultured with $8x10^4$ and $2x10^4$ fibroblasts in a collagen matrix and within a monolayer respectively.
Collagen gel contraction was quantified as a measure of fibrotic activity. CTGF and Collagen mRNA expression from gel matrices and cellular monolayers was quantified by qPCR.
Results: CD206 and $P2X_7$ expression is higher on SSc PBMC-derived macrophages (mean fluorescence 776.1 SD=409.1, 724.4 SD=455.3) compared to healthy controls (mean fluorescence 632.2 SD=73.7, 472.9 SD=25.4). There is significant correlation of CD206 expression to $P2X_7$ expression ($p<0.001$, r2=0.76) and CD206 expression is significantly correlated to Rodnan skin score ($p<0.05$, r2=0.26). $P2X_7$ expression is positively correlated to skin score. Double positive P2X7 and CD206 cells were seen in a subgroup with higher skin scores. Healthy fibroblasts co-cultured with scleroderma macrophages showed increased collagen mRNA by qPCR compared to co-culture with healthy macrophages ($p<0.01$). CTGF mRNA was positively correlated with macrophage P2X7 (r2=0.23) and CD206 (r2=0.81) expression. Preliminary work suggests contraction of collagen discs in fibroblast and macrophage co-culture is increased with SSc macrophages compared to healthy controls.
Conclusions: Data indicates a correlation between disease severity and CD206 expression by macrophages. Upregulation of CTGF and collagen expression in fibroblasts co-cultured with macrophages expressing high CD206 suggests a role for these cells in pathogenic fibrosis. The co-expression of high levels of $P2X_7$ with CD206 also indicates a possible role for the purinergic pathway in SSc fibrosis.
Future work will examine the mechanism of macrophage-fibroblast cross-talk and investigate the effect of inhibitors of CD206.
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FRIDAY, 16 JUNE 2017

Mucosal B cells: gatekeepers of immune function

OP0214 ACTIVATION STATUS OF MUCOSAL-ASSOCIATED INVARIANT T CELLS REFLECTS PATHOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Mucosal-associated invariant T (MAIT) cells are innate-like lymphocytes that express a semi-invariant TCRα chain (Vα7.2-Jα33 in humans). MAIT cells are restricted by the MHC-related molecule-1 (MR1) and uniquely recognize vitamin B metabolites presented by MR1. Like other innate-like lymphocytes, MAIT cells are also activated by cytokines in the absence of exogenous antigens. Human MAIT cells are abundant and constitute approximately 5% of peripheral blood T cells, suggesting possible roles of MAIT cells in various types of immune responses.
Objectives: We aimed to investigate whether MAIT cells are involved in systemic lupus erythematous (SLE).
Methods: Peripheral blood was collected from SLE patients and healthy volunteers. Informed consent was obtained from all individuals according to institutional ethical guidelines. Disease activity was measured based on the SLE disease activity index (SLEDAI) and a SLEDAI score $\geq$5 was defined as active disease. Peripheral blood mononuclear cells (PBMC) were stained with anti-human monoclonal antibodies against CD3, γδTCR, Vα7.2TCR, CD161, CD95 (Fas) and CD69, and then analyzed by FACS. $CD19^+$B cells or $CD14^+$monocytes were isolated from PBMC of healthy controls (HC) or SLE patients by using magnetic cell sorting. MAIT cells from healthy controls were co-cultured with B cells or monocytes in the presence of MR1 ligand (MR1L), and the expression of CD69 on MAIT cells was evaluated by FACS. Cytokine levels in plasma samples and culture supernatants were measured by ELISA and Bioplex assay. PBMC were cultured in the presence of various cytokines, and CD69 expression on MAIT cells was analyzed by FACS.
Results: The frequency of MAIT cells was markedly reduced in SLE. Reduced numbers of MAIT cells were not attributable to the downregulation of surface markers, but were partially due to the enhanced cell death of MAIT cells, possibly by activation-induced cell death. The CD69 expression levels on MAIT cells in SLE correlated with disease activity. Monocytes from patients with SLE exhibited increased ability to induce MAIT cell activation, and the profound MAIT cell activating capacity of lupus monocytes was associated with enhanced IL-12 production in the culture supernatants. The plasma concentration of IL-6, IL-18 and IFNα positively correlated with the expression levels of CD69 on MAIT cells in SLE. MAIT cells were activated by cytokines including IFNα, IL-15, and IL-12 plus IL-18 in the absence of exogenous antigens.
Conclusions: These results suggest that MAIT cells reflect the pathological condition of SLE and their activated status correlates with disease activity.

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OP0215 ROLE OF INHIBITORY IGG FC RECEPTOR IIB ON B CELLS AND MONOCYTES IN YAA-RELATED MURINE LUPUS

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Background: FcγRIIB-deficient C57BL/6 (B6) mice spontaneously develop severe lupus nephritis in combination with *Yaa* locus (TLR7-duplication).
Objectives: The aim of this study is to clarify the cell type-specific roles of FcγRIIB for the pathogenesis of *Yaa*-related lupus.
Methods: We established B cell-specific ($CD19^{Cre}$.*Yaa*), myeloid-derived cell-specific ($C/EBP\alpha^{Cre}$.*Yaa*), and dendritic cell (DC)-specific ($CD11c^{Cre}$.*Yaa*) FcγRIIB-deficient mice on B6.*Yaa* background, and compared the disease features of these mice with full FcγRIIB-deficient B6.$Fc\gamma RIIB^{-/-}$.*Yaa* mice.
Results: $CD19^{Cre}$.*Yaa* mice developed milder lupus nephritis compared to B6.$Fc\gamma RIIb^{-/-}$.*Yaa* mice, indicating that FcγRIIB deficiency on only B cells is not sufficient for the development of severe disease. Surprisingly, $C/EBP\alpha^{Cre}$.*Yaa* mice developed similar mild disease as $CD19^{Cre}$.*Yaa* mice whereas $CD11c^{Cre}$.*Yaa* stayed disease free. These observations indicate that, in B6. $Fc\gamma RIIB^{-/-}$.*Yaa* mice, FcγRIIB deficiency on both B cells and myeloid cells, but not on DCs, contribute to the development of severe lupus with high autoantibody titers. Flow cytometric analysis showed that the frequency of peripheral $Gr\text{-}1^-$, but not $Gr\text{-}1^+$, monocytes was increased and correlated positively with the frequency of splenic PNA^+ activated B cells in B6.$Fc\gamma RIIB^{-/-}$.*Yaa* and C/EBPa^{Cre}.*Yaa*, but not $CD19^{Cre}$.*Yaa*, mice. This suggests a link between FcγRIIB deficiency on monocytes, the high frequency of $Gr\text{-}1^-$ monocytes and B cell activation. Transcriptome analysis of $Gr\text{-}1^+$ and $Gr\text{-}1^-$ monocytes revealed that B cell-stimulating factor-3 (BSF-3), IL-10, and IL-1β were all up-regulated in $Gr\text{-}1^-$ monocytes.
Conclusions: FcγRIIB on B cells and monocytes controls B cell activation and autoimmune responses via different but synergistic pathways in *Yaa*-related lupus nephritis.
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PsA: the options grow!

OP0216 EFFICACY AND SAFETY OF TOFACITINIB, AN ORAL JANUS KINASE INHIBITOR, OR ADALIMUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND AN INADEQUATE RESPONSE TO CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (CSDMARDS): A RANDOMISED, PLACEBO-CONTROLLED, PHASE 3 TRIAL

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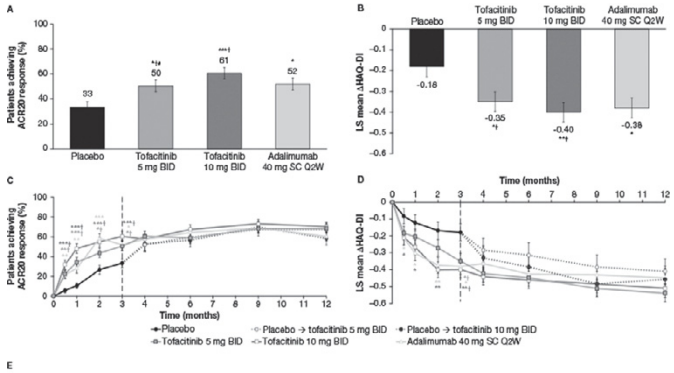
Background: Tofacitinib is an oral Janus kinase inhibitor under investigation for treatment of psoriatic arthritis (PsA).
Objectives: To assess the efficacy and safety of tofacitinib vs placebo (PBO) in patients (pts) with active PsA.
Methods: Eligible pts in this randomised, PBO- and active-controlled, 12-month Phase 3 trial had $\geq$6-months' PsA diagnosis, fulfilled CASPAR criteria, had active arthritis ($\geq$3 tender/painful and $\geq$3 swollen joints) and active plaque psoriasis at screening, inadequate response to $\geq$1 csDMARD, and were tumour necrosis factor-inhibitor (TNFi)-naïve. 422 pts were randomised 2:2:2:1:1 to tofacitinib 5 or 10 mg twice daily (BID), adalimumab 40 mg subcutaneous injection every 2 weeks, or PBO (advancing to tofacitinib 5 or 10 mg BID at Month [M]3).

Stable treatment with 1 csDMARD was required. Primary endpoints comparing tofacitinib vs PBO were ACR20 response rate and change from baseline in Health Assessment Questionnaire Disability Index (ΔHAQ-DI) at M3. Secondary endpoints included: ACR20 response rates and ΔHAQ-DI through M12; pts achieving ACR50, ACR70, ≥75% improvement of PASI and PsARC at all time points; and changes from baseline in LEI, Dactylitis Severity Score and SPARCC Enthesitis Index. Radiographic progression was assessed by van der Heijde-modified Total Sharp Score (mTSS).

Results: 96.9% of pts were white and 53.3% were female; mean age was 47.9 years. 96.2% and 88.4% of pts completed M3 and M12, respectively. At M3, tofacitinib 5 and 10 mg BID significantly improved ACR20 response rates (50.5% [p≤0.05] and 60.6% [p<0.0001] vs 33.3%; Fig 1A) and ΔHAQ-DI (-0.35 [p≤0.05] and -0.40 [p<0.001] vs -0.18; Fig 1B) vs PBO, with responses maintained to M12 (Fig 1C&D). Greater efficacy was also seen for adalimumab vs PBO. Tofacitinib 5 and 10 mg BID were superior to PBO for ACR20 response rates at Week 2 (22.4% [p<0.001] and 31.7% [p<0.0001] vs 5.7%; Fig 1C). Secondary endpoints supported primary findings (data not shown). >91% of pts were radiographic non-progressors at M12 (defined as an increase from baseline in mTSS ≤0.5). M12 safety findings were similar between groups (Fig 1E). The most common adverse events were upper respiratory tract infection (7.5–10.6%), nasopharyngitis (7.5–11.5%) and headache (3.8–10.6%).

Figure 1. A. ACR20 response rates with tofacitinib vs placebo at M3, B. ΔHAQ-DI with tofacitinib vs placebo at M3, C. ACR20 response rates up to M12, D. ΔHAQ-DI up to M12, E. Safety summary (safety analysis set; all causality)



E

	Up to M3	Up to M12				
	Placebo (N=105)	Placebo → tofacitinib 5 mg BID‡ (N=52)	Placebo → tofacitinib 10 mg BID‡ (N=53)	Tofacitinib 5 mg BID (N=107)	Tofacitinib 10 mg BID (N=104)	Adalimumab 40 mg SC Q2W (N=106)
AEs, n (%)	37 (35.2)	36 (69.2)	34 (64.2)	71 (66.4)	74 (71.2)	76 (71.7)
SAEs, n (%)	1 (1.0)	3 (5.8)	4 (7.5)	8 (7.5)	4 (3.8)	9 (8.5)
Discontinuation due to AEs, n (%)	1 (1.0)	2 (3.8)	2 (3.8)	6 (5.6)	3 (2.9)	4 (3.8)
Deaths, n (%)	0	1 (1.9)*	0	0	0	0
AEs of special interest, n (%) [day of onset]						
Serious infection	0	2 (3.8) [102, 331]	0	0	1 (1.0) [132]	1 (0.9) [170]
Herpes zoster (all non serious)	0	0	0	2 (1.9) [61, 173]	2 (1.9) [221, 317]	0
Malignancy	0	0	0	3 (2.8) [1, 11, 232]	1 (1.0) [103]	0
MACE	0	1 (1.9) [139]	0	0	0	2 (1.9) [263, 345]

Nominal *p≤0.05, **p<0.001, ***p<0.0001 vs placebo; †Achieved statistical significance at p≤0.05 per the pre-specified step-down testing procedure; dashed line indicates the end of the placebo-controlled period; ‡All patients who received ≥1 dose of study medication; §Cardiac arrest; ¶Placebo groups progressed to tofacitinib 5 mg or tofacitinib 10 mg at M3
AE, adverse event; BID, twice daily; M, month; MACE, major adverse cardiovascular event; n, number of patients with event; Q2W, every 2 weeks; SAE, serious adverse event; SC, subcutaneous

Conclusions: In TNFi-naïve pts with active PsA, tofacitinib was superior to PBO in ACR20 response rates and ΔHAQ-DI at M3, with superiority vs PBO as early as Week 2 for ACR20, which was maintained to M12. No new safety risks were identified vs previous studies in other indications.

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OP0217 USTEKINUMAB IS SUPERIOR TO TNF INHIBITOR TREATMENT IN RESOLVING ENTHESITIS IN PSA PATIENTS WITH ACTIVE ENTHESITIS- RESULTS FROM THE ENTHESIAL CLEARANCE IN PSORIATIC ARTHRITIS (ECLIPSA) STUDY

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Background: IL-23 is considered to play an important role in the development of enthesitis. Ustekinumab (UST), a combined inhibitor of IL-12/IL-23 shows efficacy in psoriatic arthritis (PsA), which is driven by enthesial and synovial disease, while it has no therapeutic role in diseases driven by synovitis alone, such as rheumatoid arthritis. We therefore speculated that inhibition of IL-23 is particularly effective in enthesitis-driven PsA patients.

Objectives: To compare the efficacy of UST with tumor necrosis factor inhibitor (TNFi) treatment in clearing enthesitis in PsA patients.

Methods: ECLIPSA is a prospective randomized-controlled open study. Patients with PsA with active enthesitis were randomized 1:1, receiving either standard doses of UST (arm 1) or TNFi (arm 2). At baseline the following parameters were assessed: age, gender, BMI, disease duration, previous DMARDs, use of corticosteroids, use of NSAIDs, swollen and tender joint count, VAS-pain, VAS-global, NAPSI, PASI, MASES, SPARCC, LDI, BASDAI, BASFI, HAQ-DI, SF-36, FACIT-F, ESR and CRP. Primary endpoint was a SPARCC of 0 after 6 months. Patients were seen every 3 months and followed for a total of 6 months. In order to investigate the effects of study treatment over time we used 2x3 mixed design ANOVA models for both physician's and patient's reported outcomes. Furthermore, exploratory logistic regression was used to predict a SPARCC of 0 at month 6 from baseline SPARCC, PASI, NAPSI, FACIT-F and BASDAI while additionally accounting for age, gender, PsA duration and study treatment.

Results: 51 patients (UST=25; TNFi=26) were screened and 47 patients (UST=23; TNFi=24) were enrolled with 4 patients not presenting signs of active enthesitis at baseline. Mean ± SD age was 59.11±12.16 years and mean ± SD disease duration was 6.4±7.79 years. Mean± SD SPARCC at baseline was 4.87±2.69 in the UST group and 3.88±2.52 in the TNFi group. Other baseline characteristics were similar between both groups with exception of HAQ-DI, BASFI and SF-36 mental scale. In regards to the effect of study treatment (TNFi vs. UST) and time, the corresponding ANOVAs suggested an important interaction of both factors for measures of enthesitis (MASES and SPARCC), patient-reported disease activity (BASDAI and BASFI), physical well-being (SF-36 physical component summary scale), and PASI all p≤0.044 with superiority of UST. However, TNFi was superior to UST with respect to improvement of fatigue (FACIT-F), p<0.001. After 6 months, 17 out of 24 UST patients (70.8%) and 10 out of 26 TNFi patients (38.4%) reached the primary endpoint (SPARCC=0). Logistic regression predicting enthesitis-free state of disease was significantly related to study treatment only, with patients receiving UST being more likely to show no signs of enthesitis at month 6 (OR=0.037; p=0.005).

Conclusions: These results show that UST is superior to TNFi in resolving the enthesitis component of disease in PsA patients with active enthesial disease. Based on these data more stratified treatment approaches can be designed in PsA patients, where enthesitis-driven patients are targeted by IL-23/IL-17 pathway inhibitors, while more systemic disease manifestations of PsA, such as patients with polyarticular disease or those with high-level fatigue are targeted by TNFi.

Disclosure of Interest: None declared

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OP0218 EFFICACY AND SAFETY RESULTS OF GUSELKUMAB, AN ANTI-IL23 MONOCLONAL ANTIBODY, IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS OVER 24 WEEKS: A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Objectives: To evaluate the efficacy, safety, and tolerability of guselkumab (GUS), a fully human monoclonal antibody against the p19 subunit of IL-23, in patients (pts) with active psoriatic arthritis (PsA).

Methods: In this double-blind, placebo-controlled, multicenter study, pts with active PsA and ≥3% body surface area (BSA) of plaque psoriasis despite current or previous treatment with standard-of-care therapies, including those previously exposed to anti-TNFα agents, were randomized 2:1 to receive GUS 100 mg subcutaneously (SC) or placebo (PBO) at wks 0, 4, and every 8 wks (q8w) thereafter through wk44. At wk16, pts from either group with <5% improvement from baseline in both swollen and tender joint counts were eligible for early escape to open-label ustekinumab. At wk24, all remaining PBO pts crossed-over to receive GUS 100 mg, and then received GUS at wk28, and q8w thereafter through wk44. The primary endpoint was ACR 20 response at wk24. Major