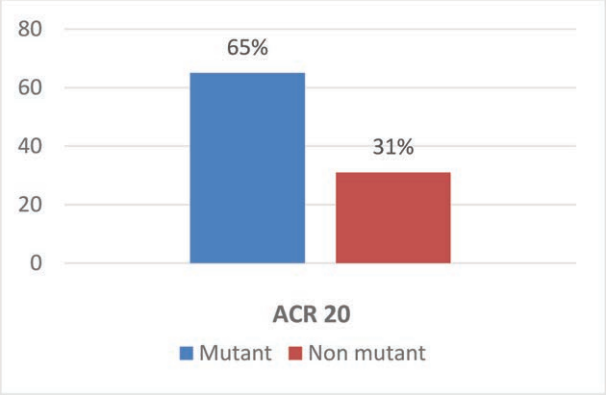

Figure 1.

JAK2 mutation and ACR20 after **Baricitinib treatment.**
Acknowledgements: NIL.
Disclosure of Interests: None Declared.
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Impact of sex on disease pathogenesis and outcome

POS0359

SEX-RELATED INEQUITY IN RANDOMIZED CONTROLLED TRIALS IN PSORIATIC ARTHRITIS: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

Keywords: Psoriatic arthritis, Spondyloarthritis, Clinical Trials

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Background: Sex is an important determinant of health including response to therapy. Limited information exists on representation and reporting of results by sex in randomized controlled trials (RCTs) in patients with psoriatic arthritis (PsA).
Objectives: Through a systematic literature review and meta-analysis of RCTs in PsA, we aimed to assess potential health inequities in sex-related dimensions by describing the proportion of trials reporting sex-disaggregated data and by comparing the efficacy of advanced therapies between male and female participants.
Methods: We performed a systematic literature search of Medline, Embase and Central databases, and conference abstract archives from January 1, 2000 to June 30, 2022. We included RCTs that reported sex-disaggregated results and assessed the efficacy of an advanced therapy (biologic or targeted synthetic) in adult participants with PsA. Efficacy end points included the proportion of participants achieving minimal disease activity (MDA) or meeting the American College of Rheumatology 20 (ACR20) and ACR50 response criteria at the primary endpoint of the trial. We used random-effect models to calculate pooled effects for responses in males vs. females for the different classes of advanced therapies (Odds Ratio (OR) and 95% Confidence interval (CI)).
Results: We included a total of 52 RCTs, accounting for 21,769 participants, in the review. An equal participation of male and female patients was found (50.1% male participants). Only 9 trials (17.3%, 5,604 participants) reported sex-disaggregated baseline characteristics, 16 trials (30.7%, 9,028 participants) reported sex-disaggregated efficacy endpoints and 2 trials (3.8%, 1,005 participants) reported sex-disaggregated safety endpoints. Female patients had significantly higher baseline tender joint count, Health Assessment Questionnaire Disability Index, physician and patient global assessment of disease activity and pain scores. Male patients had significantly higher baseline psoriasis area and severity index (PASI) and CRP. Differences in pooled estimates of efficacy endpoints were evident for male and female patients across the different classes of advanced therapies. The probability of achieving ACR20 responses was significantly higher in male vs. female patients for IL-17 inhibitors (i) (OR 1.76, 95% CI 1.33, 2.34), IL-23i (OR 1.46, 95% CI 1.20, 1.78), IL-12/23i (OR 2.66, 95% CI 1.39, 5.09) and TNFi (OR 1.67, 95% CI 1.20, 2.34), but not for JAKi (OR 1.10, 95% CI 0.87, 1.38). [**Figure 1A**] Similarly, the probability of achieving ACR50 responses was significantly higher in males vs. females with all advanced therapies, except JAKi (OR 1.09, 95% CI 0.73, 1.62) **[Figure 1B]**. The probability of achieving MDA was higher in males across all classes of advanced therapies, including IL-17i (OR 1.99, 95% CI 1.50, 2.63), IL-23i (OR 1.79, 95% CI 1.29, 2.50), TNFi (OR 2.62, 95% CI 1.54, 4.44) and JAKi (OR 1.77, 95% CI 1.15, 2.73) and IL-12/23i (OR 1.82, 95% CI 0.97, 3.40). Male and female patients had similar probabilities for achieving ACR20 responses when using placebo (OR 1.04, 95% CI 0.86, 1.27).
Conclusion: Based on the reported results, female patients participating in RCTs are less likely to achieve efficacy end points for most classes of advanced therapies. Some differences in responses were found across classes of advanced therapies. RCTs should report sex-disaggregated results to identify sex-related differences in efficacy and safety outcomes which will inform patient-centered therapeutic strategies.

(A) ACR20 Response

Class of medication	Study	Medication, dose interval	Endpoint (weeks)	Relative Weight (%)	Odds Ratio, 95%CI
csDMARD	SEAM-PsA	MTX	24	100	1.07 (0.67, 1.71)
Total					**1.07 (0.67, 1.71)**
TNFi	EXCEED	ADA 40mg q2w	52	19.4	2.23 (1.50, 3.32)
TNFi	OPAL Broaden+Beyond	ADA 40mg q2w	12	10.8	1.07 (0.48, 2.35)
TNFi	RAPID-PsA	CER 200mg q2w	24	16.7	1.41 (0.85, 2.34)
TNFi	SEAM-PsA	ETA 50mg qw	24	17.3	1.00 (0.62, 1.61)
TNFi	SEAM-PsA	ETA 50mg qw + MTX	24	16.9	1.80 (1.10, 2.95)
TNFi	SELECT-PsA 1	ADA 40mg q2w	12	18.9	2.82 (1.86, 4.27)
Total					**1.67 (1.20, 2.34)**
IL-17i	EXCEED	SEC 300 mg q4w	52	46.5	1.82 (1.21, 2.75)
IL-17i	SPIRIT P1+P2	IXE 80 mg q2w	24	26.5	1.94 (1.12, 3.35)
IL-17i	SPIRIT P1+P2	IXE 80 mg q4w	24	27.0	1.52 (0.88, 2.61)
Total					**1.76 (1.33, 2.34)**
IL-23i	COSMOS	GUS 100mg q8w	24	11.7	1.39 (0.78, 2.47)
IL-23i	DISCOVER-1+2	GUS 100 mg q4w	24	21.8	1.66 (1.09, 2.54)
IL-23i	DISCOVER-1+2	GUS 100 mg q8w	24	22.6	1.43 (0.94, 2.16)
IL-23i	KEEPsAKE 1+2	RIS 150mg	24	43.9	1.41 (1.04, 1.89)
Total IL-23i					**1.46 (1.20, 1.78)**
IL-12/23i	MUST	UST+MTX	24	53.8	2.46 (1.02, 5.96)
IL-12/23i	MUST	UST+PBO	24	46.2	2.92 (1.12, 7.57)
Total					**2.66 (1.39, 5.09)**
JAKi	NCT03881059	DEUC 6 mg qd	16	5.1	0.50 (0.18, 1.37)
JAKi	NCT03881059	DEUC 12 mg qd	16	5.7	0.76 (0.38, 1.98)
JAKi	OPAL Broaden+Beyond	TOF 5mg + 10mg	12	37.1	1.09 (0.75, 1.58)
JAKi	SELECT-PsA 1	UPA 15 mg qd	12	28.8	1.32 (0.87, 2.02)
JAKi	SELECT-PsA 1	UPA 30 mg qd	12	23.3	1.14 (0.71, 1.82)
Total					**1.10 (0.87, 1.38)**

(B) ACR50 Response

Class of medication	Study	Medication, dose interval	Endpoint (weeks)	Relative Weight (%)	Odds Ratio, 95%CI
TNFi	EXCEED	ADA 40mg q2w	52	52.3	2.55 (1.72, 3.78)
TNFi	OPAL Broaden+Beyond	ADA 40mg q2w	12	12.5	1.33 (0.58, 3.04)
TNFi	RAPID-PsA	CER 200mg q2w	24	35.3	2.02 (1.24, 3.28)
Total					**2.17 (1.62, 2.90)**
IL-17i	EXCEED	SEC 300 mg q4w	52	49.9	1.63 (1.11, 2.39)
IL-17i	SPIRIT P1+P2	IXE 80 mg q2w	24	24.6	2.39 (1.38, 4.12)
IL-17i	SPIRIT P1+P2	IXE 80 mg q4w	24	25.5	2.26 (1.33, 3.86)
Total					**1.95 (1.49, 2.55)**
IL-23i	DISCOVER-1+2	GUS 100 mg q4w	24	50.2	1.80 (1.15, 2.80)
IL-23i	DISCOVER-1+2	GUS 100 mg q8w	24	49.8	1.63 (1.05, 2.54)
Total					**1.71 (1.25, 2.34)**
IL-12/23i	MUST	UST+MTX	24	54.5	1.70 (0.71, 4.08)
IL-12/23i	MUST	UST	24	45.6	3.71 (1.39, 9.95)
Total					**2.43 (1.14, 5.20)**
JAKi	OPAL Broaden+Beyond	TOF 5mg + 10mg	12	100	1.09 (0.73, 1.62)
Total					**1.09 (0.73, 1.62)**

Figure 1. Random-effects meta-analysis of the efficacy of advanced therapies, by (A) ACR20, (B) ACR50 response between male and female patients with psoriatic arthritis. CI, confidence interval; ACR, American College of Rheumatology; ADA, Adalimumab; DEUC, Deucravacitinib; CER, Certolizumab; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ETA, etacercept; GUS, Guselkumab; IL-17i, interleukin-17 inhibitor; IL-12/23i, interleukin-12/23 inhibitor; IL-23i, interleukin-23 inhibitor; IXE, Ixekizumab; JAKi, janus kinase inhibitor; MTX, methotrexate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RIS, Risankizumab; SEC, secukinumab; TOF, Tofacitinib, TNFi, tumour necrosis factor inhibitor; UPA, Upadacitinib; UST, Ustekinumab.

REFERENCES: NIL.
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POS0360

X-CHROMOSOME DOSAGE, RATHER THAN THE GONADAL SEX ITSELF, MAJORLY CONTRIBUTES TO SEX BIAS IN AUTOIMMUNITY IN HUMANS

Keywords: Autoantibodies, Gender/diversity issues

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Background: Most autoimmune diseases exhibit a profound female sex bias. Mechanisms underlying this sexual dimorphism remain unclear. We previously reported that the XX sex chromosome complement, as compared to XY, imparts greater susceptibility to autoimmune diseases such as lupus in experimental models (Smith-Bouvier D, et al, J Exp Med 2008). Gonadectomized XX female

mice had more anti-DNA antibodies, autoimmune pathology, and mortality than XY female (Sry^{ko}) mice. Similarly, gonadectomized XX male (Sry^{Tg}) mice had more severe autoimmune disease than XY male ($Sry^{ko}Sry^{Tg}$). To begin to translate these murine findings onto humans, we asked if sex chromosome dosage plays a role in predisposition to autoimmunity.

Objectives: To test the hypothesis that X chromosome dosage, rather than the female sex itself, imparts susceptibility to autoimmunity in humans.

Methods: We administered autoimmune disease and connective tissue disease questionnaires and analyzed serum autoantibody levels in males and females with sex chromosome aneuploidy including males with two X chromosomes (XX males, including Klinefelter's syndrome) and females with one X chromosome (X0 females, including Turner's syndrome) and their respective male and female controls with normal sex chromosome numbers.

Results: Levels of IgG anti-chromatin, anti-nucleosome and anti-histone (H2A, H2B and H3) autoantibodies were significantly higher in XX males (47,XXY; 48,XXYY, and mosaics) compared to 46,XY men. XX males, however, did not have non-specific B cell hyper-reactivity, as the levels of anti-thyroid peroxidase antibody that is associated with autoimmune thyroiditis were similar between the two groups and antibodies against intrinsic factor which are present in patients with autoimmune gastritis/pernicious anemia were reduced in XX males than in XY males. In contrast to the increased frequency of autoantibodies against systemic autoantigens in XX males vs. XY males, such autoantibodies were reduced in X0 females as compared to XX females. However, autoantibodies against organ-specific autoantigens such as thyroid and gliadin were higher in X0 females than in XX females. A preliminary analysis of clinical questionnaire revealed an increase in autoimmune conditions in XX males when compared with known population prevalence of these diseases. Preliminary immune phenotyping of peripheral blood cells conducted thus far show altered frequency and/or function of natural killer T-cells, CD8+ T cells or IL-4/IL-17 producing cells in individuals with sex chromosome aneuploidy compared to their respective controls.

Conclusion: These data suggest that humans with two X chromosomes as compared to those with one X chromosome, regardless of their gonadal sex, exhibit increased susceptibility to systemic autoimmunity. Preliminary evidence also suggests a differential regulation of systemic versus organ-specific autoimmunity in persons with sex chromosome aneuploidy.

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Disclosure of Interests: None Declared.

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POS0361 COMPREHENSIVE TRANSCRIPTOMIC CHARACTERIZATION REVEALS CORE GENES AND MODULES ASSOCIATED WITH SEX-DEPENDENT MOLECULAR PAIN MECHANISMS IN OSTEOARTHRITIS

Keywords: Pain, Gender/diversity issues, Osteoarthritis

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Background: Female sex is identified as a key nonmodifiable risk factor in the development of OA, particularly after the age of 55. Additionally, women appear to have a lower threshold for pain and present with more chronic pain conditions than men. Our previous studies demonstrated that female mice develop pain at the same time as male mice despite having reduced levels of joint damage, indicating the existence of sex-dependent mechanisms for the induction of pain. In non-arthritis murine pain models, different immune cells in the dorsal root ganglia (DRG) appear to contribute to sex-dependent differences in sensitization. Furthermore, we have recently uncovered cellular and molecular differences between immune cells and inflammatory profiles in the DRGs and joints of male and female mice with collagen antibody-induced arthritis.

Objectives: Search for putative pain pathways and associated temporal patterns in male and female mice subjected to surgically induced OA.

Methods: C57BL/6 male and female mice (10-week-old, n=5 per group, i.e., surgery, sex, and timepoint) were randomized subjected to either sham surgery or partial meniscectomy (PMX). Static weight bearing measurements were performed using a Linton Incapacitance Tester. Mice underwent a 2-week acclimatization post-surgery, followed by weekly measurement between week 5 to 12. L3-L4 DRGs were harvested for RNA sequencing at week 6, 10 and 12 post-surgery. The Weighted Gene Co-expression Network Analysis (WGCNA) package in R was used to construct a signed co-expression network from the expression data.

Results: Considering all groups, a tendency to pain-related behavior was observed at week 10 post-surgery, and a statistically significant difference in weight bearing found at week 12 when the PMX group was compared with sham group. We performed WGCNA to identify modules that were related to surgery and sex using 6-, 10-, and 12-week samples, respectively. For the 6-week network, 14 modules were identified. Only associations with sex were observed, with 3 modules positively related with male and 1 module positively related with female. For the 10-week network, 14 modules were identified. 6 modules were related by single trait, 3 of which were positively related with male, 2 of which were positively related with PMX, and 1 of which weas negatively related with PMX. In addition, 1 module was related with both surgery and sex, whereby it was negatively related with PMX and positively with being female. For the 12-week network, 19 modules were identified. Most significant associations were observed only with PMX, where 5 modules showed positive associations and 3 modules showed negative associations. Furthermore, greenyellow module was related with both surgery and sex, positively related with PMX and being female. As a result, this module was chosen to investigate further. According to the threshold (MM > 0.8 and GS > 0.2), 102 candidate hub genes were obtained in this module. When PPI analysis was performed, 14 candidate hub genes (top 5%, ranked by the MCC scoring method) were obtained. In total, 9 overlapping genes (Npy, Tac1, Calca, Gap43, Bdnf, Shc1, Ngfr, Casp3 and Jun) were identified as hub genes. The enriched biological process was 'neurotrophin TRK receptor signaling pathway'. And the enriched KEGG pathway were 'neurotrophin signaling pathway' and 'MAPK signaling pathway'.

Conclusion: This study reveals sex, disease and time-dependent changes in the DRG transcriptome during the development of painful OA. Importantly, our findings highlight a distinct TrkA and neurotrophin signaling signature that is evident at 12 weeks post-surgery only in OA-induced pain-related behaviors in female mice.

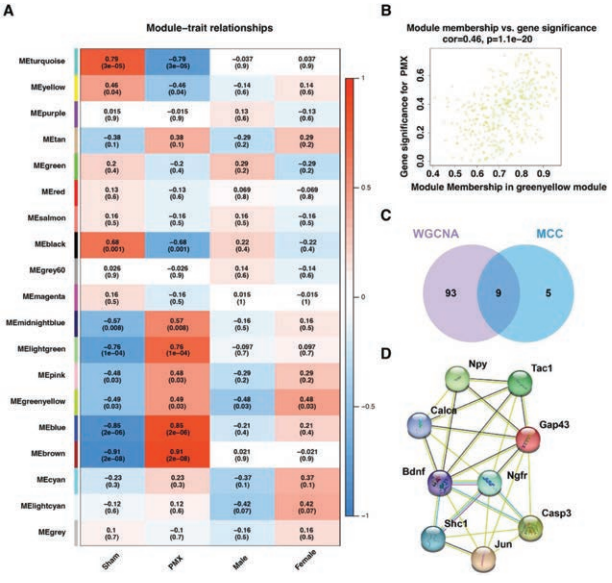

Figure 1. The construction of DRG transcriptomic gene network by WGCNA for week 12 post-surgery. (A) Association between modules and sample trait data. (B) The MM versus GS scatterplot for PMX in greenyellow module. (C)Venn diagram of the identified hub genes. (D) PPI network visualization of hub genes by Maximal Clique Centrality (MCC).

REFERENCES: NIL.

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