Mechanisms and Predictors of Aromatase Inhibitor-associated MusculoSkeletal Symptoms: The ZAP Trial

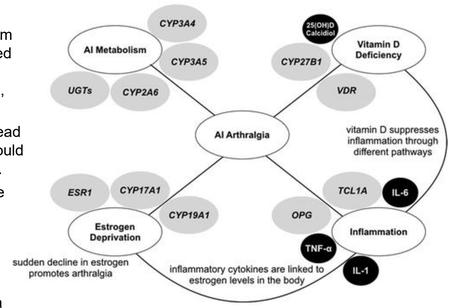
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Introduction

- Patients receiving aromatase inhibitors (AIs) often suffer from Aromatase Inhibitor-Associated Musculoskeletal Symptoms (AIMSS), defined as myalgias, arthralgias, or joint stiffness.
- These adverse effects often lead to drug discontinuation and could thus impact cancer outcomes.
- We conducted the prospective single arm Zoledronic Acid Prophylaxis (ZAP) trial, which demonstrated that zoledronic acid administered prior to initiating letrozole and after 6 months was associated with a reduced incidence of AIMSS compared to historical controls (BCRT 2018).



- We hypothesize that alterations in muscle injury, vitamin D deficiency, inflammation and estrogen deprivation may be associated with AIMSS.

Objectives

- To evaluate alterations in biomarkers of interest (CK-MB, vitamin D, cytokines and estradiol) that may indicate those with greater reduction in AIMSS with administration of AI and ZAP.

Methods

- Participants from ZAP were postmenopausal women with stage 0-III breast cancer receiving adjuvant letrozole, who also received zoledronic acid at study entry and 6-months.
- Blood samples were obtained at baseline and 6 months. Blood-based correlatives included serial assessments of 25-OH vitamin D, CK-MB, a multiplex cytokine array, and estradiol.
- At baseline we collected whole blood for pharmacogenomic analysis SNPs in a target genes list.
- AIMSS was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI) and Visual Analog Scale (VAS) at 6 months. AIMSS was defined as an increase of 0.22 in a scale of 0-3 in the HAQ-DI and/or an increase of 2.0 cm in a scale of 10 cm in the VAS.
- We evaluated other patient reported outcomes (PROs): depression (CESD), anxiety depression (HADS-A), hot flashes (HFRDI), menopausal symptoms (NSABP-MSQ), sleep quality (PSQI), and quality of life (EuroQol).
- Data will be summarized using descriptive statistics. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by proportions.
- Pearson's correlation or Spearman's rank correlation will be reported when appropriate as an evaluation of the association between different variables.
- For the primary analysis, absolute value of biomarkers and the change in biomarker values from baseline at different timepoints will be summarized and reported. Student's t-test, or Wilcoxon rank sum test when normality cannot be achieved, will be conducted to compare the biomarker values or changes from baseline between AIMSS groups.
- Furthermore, logistic mixed-effects models will be used to analyze the association between AIMSS status and the biomarker values and changes in the biomarker values over time.
- ROC analysis evaluated the predictive accuracy of biomarker changes for AIMSS. Pearson correlation assessed inter-biomarker correlations.

Results

Table 1: Participant Demographics Stratified by AIMSS

	AIMSS = Yes (N=22)	AIMSS = No (N=22)	P-value
Age			
Mean (SD)	61.0 (7.2)	59.8 (7.6)	0.64
Min - Max	47.0 - 81.0	45.0 - 74.0	
Race			
White	20 (90.9%)	21 (95.5%)	1
Non-White	2 (9.1%)	1 (4.5%)	
Ethnicity			
NHNL	22 (100%)	22 (100%)	
BMI			
Mean (SD)	30.4 (7.4)	28.4 (6.2)	0.39
Min - Max	19.2 - 48.4	19.3 - 45.9	
Missing	1 (4.5%)	0 (0%)	
Arthritis			
Yes	11 (50.0%)	10 (45.5%)	1
No	11 (50.0%)	12 (54.5%)	
Hormone Replacement Therapy			
Yes	12 (54.5%)	8 (36.4%)	0.22
No	8 (36.4%)	14 (63.6%)	
Missing	2 (9.1%)	0 (0%)	
Taxane			
Yes	7 (31.8%)	4 (18.2%)	0.49
No	15 (68.2%)	18 (81.8%)	
Stage			
0	1 (4.5%)	1 (4.5%)	0.49
1	10 (45.5%)	14 (63.6%)	
2	7 (31.8%)	6 (27.3%)	
3	4 (18.2%)	1 (4.5%)	

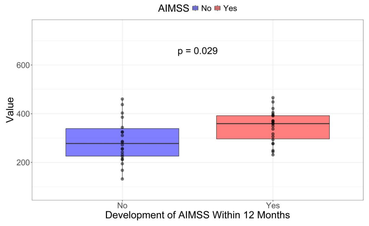
Table 2: Baseline and Changes in 6-month Cytokines Stratified by AIMSS

	AIMSS = Yes (N=22)	AIMSS = No (N=22)	P-value
Baseline MCP1			**0.03**
Mean (SD)	346.7 (65.8)	323.8 (206.4)	
Min - Max	231.0 - 465.9	131.8 - 1165.8	
Baseline MCP4			
Mean (SD)	237.6 (125.4)	181.6 (76.5)	**0.03**
Min - Max	109.3 - 699.1	102.6 - 466.4	
Absolute Change of CK-MB			
Mean (SD)	-0.1 (0.5)	0.2 (0.6)	0.37
Min – Max	-1.1 - 0.8	-0.7 - 1.3	
Missing	7 (31.8%)	8 (36.4%)	
Absolute Change of Vitamin D			
Mean (SD)	-1.2 (6.8)	-0.8 (9.6)	0.95
Min – Max	-13.0 - 11.0	-17.0 - 25.0	
Missing	7 (31.8%)	6 (27.3%)	
Relative Change of IL5	N=15	N=37	**0.03**
Mean (SD)	5333.2 (20655.7)	-0.3 (0.8)	
Min – Max	-0.9 - 79999.0	-1.0 - 3.0	

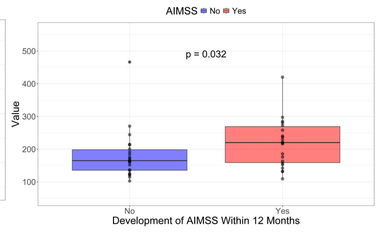
- **From 2011 to 2013, 59 women enrolled in ZAP. Samples were collected in 59 and 49 participants at baseline and 6 months, respectively.**
- **There were no significant differences in baseline characteristics between those with or without AIMSS at any time point.**
- **MCP1 and MCP4 were higher at baseline in those who developed AIMSS.**

Figure 1: Boxplots of baseline and changes in biomarker values stratified by presence of AIMSS

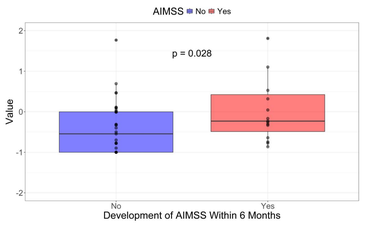
(A) Measurement of MCP1 at baseline



(B) Measurement of MCP4 at baseline

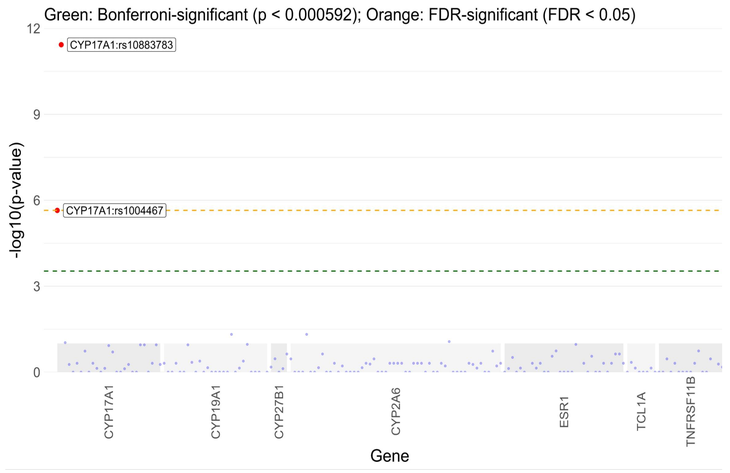


(C) Relative change in the value of IL5



- **Those with higher MCP1 and MCP4 at baseline (Panel A) and increased IL5 after 6 months (Panel B) were likely to report AIMSS.**

Figure 2: SNP Associations with AIMSS



The significant changes in SNPs were in CYP17A1, a gene that encodes a member of the cytochrome P450 enzymes. The cytochrome P450 proteins catalyze reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. It is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, androgens and estrogens.

Conclusions & Future Directions

- Inflammation (increases in MCP1 and TNF-alpha) was associated with the reporting of AIMSS.
- Early changes in cytokines profile may identify those at greater risk for AIMSS and who may derive greater benefit from earlier symptom management to prevent discontinuation.
- Estradiol testing and analyses are pending and will be shared in future presentation.
- Use of zoledronic acid may reduce level of expression of cytokines, such as TNF-beta.
- Further studies are needed to validate these cytokines as early biomarkers for the development of AIMSS.

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