Sulindac Improves Stiffness and Quality of Life in Women Taking Aromatase Inhibitors for Breast Cancer

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Background

- Early discontinuation/incomplete adherence to aromatase inhibitors (AI) for postmenopausal hormone receptor positive (HR+) breast cancer is common and increases risk of recurrence.
- Development of AI-induced musculoskeletal symptoms (AIMSS) is a major risk factor for poor adherence.
- Mechanisms of AIMSS include increased inflammation as well as enhanced pain perception.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for treating AIMSS on limited evidence of benefit.
- Sulindac is a non-selective NSAID used to treat arthritis.

Objectives

Among postmenopausal, HR+ breast cancer patients on AI therapy non-randomly assigned to either twice daily 150 mg oral sulindac (n=50) or observation (n=56) for 12 months:

1. Assess change in MSS severity assessed using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and Brief Pain Inventory Short Form (BPI-SF).
2. Assess change in The Functional Assessment of Cancer Therapy – General form (FACT-G) was used to measure QOL.

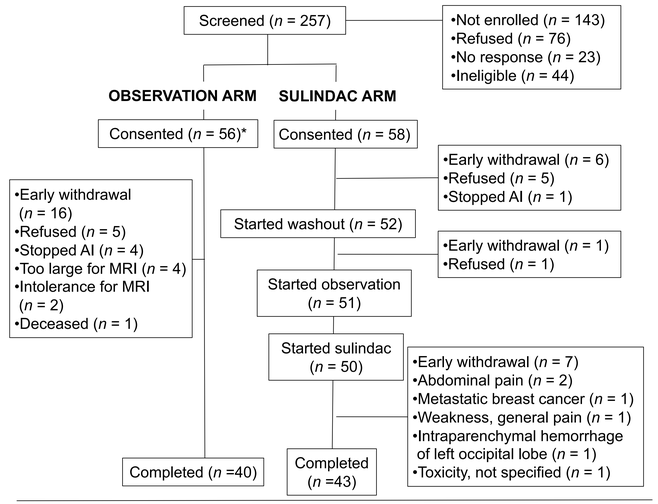
Table 1. Baseline characteristics of Sulindac and Observation Arms.[1]

Characteristic	Sulindac (n = 50)	Observation (n = 50)
Age at enrollment (y), mean ± SD	62.2 ± 5.4	64.3 ± 6.7
Time on AI (months), median (IQR)	12.5 (7.2, 33.4)	11.9 (5.0, 22.2)
BMI (kg/m^2), mean ± SD	27.5 ± 5.2	28.1 ± 5.3
Race/ethnicity, n (%)		
Non-Hispanic White	44 (88.0)	46 (93.9)
Hispanic	3 (6.0)	3 (6.1)
Other	3 (6.0)	0 (0.0)
Education, n (%)		
Some High school or graduate	10 (20.0)	14 (28.50)
College or higher	40 (70.0)	35 (71.5)
Disease stage, n (%)		
0-I	32 (64.0)	33 (66.0)
II-III	18 (36.0)	17 (34.0)
Aromatase inhibitor therapy, n (%)		
Anastrozole	32 (64.0)	41 (82.0)
Letrozole	13 (26.0)	8 (16.0)
Exemestane	6 (12.0)	0 (0.0)
NSAID/Pain Medication, n (%)		
Low-dose aspirin or NSAID (PRN)[2]	13 (26.0)	16 (32.0)
Other pain medication	8 (16.0)	10 (20.0)

[1] Baseline in the AI + Sulindac group defined as the post-observation visit

[2] Includes one patient in observation reporting daily use of 325 mg ASA, all others 81 mg ASA

Figure 1. Study Consort



* Includes 5 participants originally consented to sulindac arm that switched to observation

Table 2. Mean difference in WOMAC, BPI-SF, FACT-G scores at 6 and 12 months from baseline. [1, 2, 3]

	n	Baseline (95% CI)	Difference 6 months [95% CI]	P-value	Difference 12 months [95% CI]	P-value
Sulindac						
WOMAC Total	50	22.89 [17.25, 28.53]	-3.79 [-7.53, -0.05]	0.047	-5.85 [-9.73, -2.00]	**0.003**
BPI-SF Worst Pain	50	3.35 [2.58, 4.11]	-0.32 [-1.11, 0.48]	0.465	-0.34 [-1.17, 0.49]	0.421
FACT-G Total	50	89.58 [86.09, 93.08]	1.47 [-1.15, 4.08]	0.271	3.06 [0.34, 5.79]	**0.028**
Observation						
WOMAC Total	50	13.05 [8.82, 17.28]	1.89 [-1.02, 4.81]	0.20	-0.25 [-3.20, 2.69]	0.87
BPI-SF Worst Pain	50	2.32 [1.66, 2.98]	-0.04 [-0.77, 0.68]	0.91	-0.29 [-1.01, 0.43]	0.43
FACT-G Total	50	90.88 [86.45, 95.31]	2.20 [-0.82, 5.22]	0.15	-0.82 [-3.87, 2.23]	0.60

[1] Adjusted for age, BMI, time on AI, and pain medication use

[2] Not shown, change at 3 months with sulindac were not significant and change at 9 months were similar to 12 months

[3] Change in MSS/QOL across time was assessed in each group separately using linear mixed effects models

Table 3. Mean difference in WOMAC, BPI-SF, FACT-G scores at 6 and 12 months from baseline in patients with elevated MSS.[1,2, 3]

	n	Baseline (95% CI)	Difference 6 months [95% CI]	P-value	Difference 12 months [95% CI]	P-value
Sulindac						
WOMAC Total Score	25	38.34 [31.55,45.14]	-10.67 [-15.59, -5.75]	<0.0001	-15.79 [-21.04, -10.53]	**<0.0001**
BPI-SF Worst Pain	25	4.77 [3.72, 5.82]	-0.99 [-2.01, 0.04]	0.060	-1.39 [-2.51, -0.27]	**0.015**
FACT-G Total Score	25	84.15 [79.26, 89.05]	3.48 [-0.35, 7.31]	0.075	6.18 [2.08, 10.27]	**0.003**
Observation						
WOMAC Total Score	14	33.18 [26.64, 39.71]	-2.58 [-9.71, 4.56]	0.48	-2.36 [-9.87, 5.15]	0.54
BPI-SF Worst Pain	14	4.36 [3.21, 5.50]	0.17 [-1.38, 1.71]	0.83	1.28 [-0.35, 2.90]	0.12
FACT-G Total Score	14	80.70 [72.28, 89.13]	1.19 [-5.58, 7.97]	0.73	-4.85 [-11.95, 2.25]	0.18

[1] Adjusted for age, BMI, time on AI, and pain medication use

[2] *Data not shown for Sulindac include changes at 3 and 9 months that were significant*

[3] Change in MSS/QOL across time was assessed in each group using linear mixed effects models

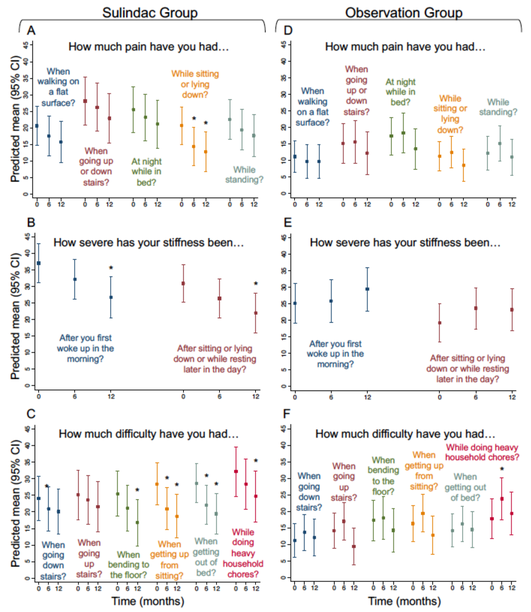


Figure 2. Change in response to individual WOMAC subscale specific questions over time by study group. Results for Sulindac and Observation arms are shown in Panel A-C and D-F, respectively for all 5 WOMAC pain items, 2 WOMAC stiffness items and for 5 WOMAC physical function items with highest baseline symptom severity.
* P < 0.05

Summary of Findings

- At baseline, 40% of patients enrolled to the sulindac arm reported moderate-to-high MSS severity in at least 1 WOMAC scale compared to 22% in the observation arm.
- Moderate-to-severe stiffness, rather than pain, was the most common symptom reported in both study arms.
- After 12 months, the proportion of patients receiving sulindac with moderate-to-high MSS severity reduced to 18.6%
- Sulindac arm participants also experienced significant declines in Total WOMAC and all three WOMAC subscale scores.
- There were no changes in any WOMAC, BPI-SF, or FACT-G scores in the observation group.
- With sulindac, mean improvements (decreases) of 15.9 points in WOMAC physical function and 20.5 points for WOMAC stiffness meet consensus for minimal clinically important improvement.

Conclusions

- The findings of a significant improvement in MSS severity among patients on AI therapy with sulindac should be interpreted with caution in the absence of a placebo control.
- Positive effects of sulindac on MSS severity in patients on AI therapy implicate a role for eicosanoids in AI induced MSS.
- Further examination of NSAIDs including dose and duration for effective management of AIMSS, including conduct of randomized controlled trial, are warranted.

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