Randomized Multicenter Placebo Controlled Trial of Omega-3 Fatty Acids for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain: SWOG S0927

BACKGROUND:

- Although Aromatase Inhibitors (AI) have well-proven efficacy for the treatment of hormone sensitive breast-cancer, arthralgia's are the most common adverse effects and can result in decreased quality of life and discontinuation of therapy. Currently there are no proven treatments for AI related arthralgia.
- Several studies have suggested that patients receiving Omega-3 Fatty Acids (O3-FA) have fewer symptoms of rheumatoid arthritis (RA).

OBJECTIVE:

- To test the hypothesis that O3-FA's reduce pain and stiffness in women undergoing adjuvant AI therapy for early-stage breast cancer

METHODS:

- **Design**: Multicenter, randomized, double blind placebo controlled parallel trial; Duration: 24 mo.
- **Inclusion criteria**: Postmenopausal women with a history of stage I-III hormone sensitive breast cancer receiving adjuvant AI therapy for > 90 days with a score > 5 of 10 on the Brief Pain Inventory–Short Form (BPI-SF) worst pain/stiffness measure (item 2) who reported that the symptoms started or worsened after initiation of AI therapy and they were required to have a Zubrod performance status of 0-2.
- **Exclusion criteria**: Women who received O3-FA supplements within 3 months before enrollment; Had a history of fracture or surgery involving the affected joint within the prior 6 months; Received oral narcotics or topical analgesics within the prior 14 days; Received oral steroids or intra-articular steroid injections within the prior 28 days
- **Primary outcome measure**: The worst pain (item 2) on the BPI-SF general pain scale at 12 weeks
- **Secondary outcome measures**: BPI worst pain scores at weeks 6 and 24. Also, outcomes in the mean change for the M-SACRAH, WOMAC, FACT-ES, and global rating of change scales were assessed at weeks 6, 12, and 24.
- 249 patients received either
    - Omega-3 Fatty Acid 3.3 g/day (each capsule contained 560 mg of EPA + DHA in a 40-to-20 ratio
      OR
    - Placebo (each capsule contained a blend of soybean and corn oil)
      *Patients in either group were instructed to take 6 capsules/day
- Power 90% with a stipulated two sided alpha level of 0.05 and an estimated 5% non-adherence and 20% dropout rate at the primary endpoint evaluation time of 12 weeks. For a 2 point difference and 3.5-point standard deviation at 12 weeks with other parameters specified, 222 eligible patients were required for 90% power under a two-arm normal design
- Data handling method was intent-to-treat with imputation of data

RESULTS:

- 209 patients were considered analyzable for the primary outcome measure (102 in O3-FA arm and 107 in placebo arm)
- **Primary outcome measure**: The mean observed BPI worst pain score was 1.74 points lower (reduced pain) at 12 weeks compared with baseline in the O3-FA arm and 1.49 points lower in the placebo arm. In a multivariable analysis, adjusted week-12 BPI worst pain scores were 0.17 points lower on average (implying slightly less pain) in O3-FA vs. placebo (95% CI, -0.79 to 0.44; P = .58).
- **Secondary outcome measures**: The mean observed change in the M-SACRAH, WOMAC measures reflected somewhat reduced symptoms in the O3-FA arm compared with placebo at each of the

assessment times but somewhat increased symptoms when using the FACT-ES measure however; there was no evidence that any of these differences were statistically significant.

- **Author's conclusion:** A substantial (> 50%) and sustained improvement was found in AI arthralgia for both O3-FA's and placebo but a meaningful difference between groups was not found.

STRENGTHS:

- Placebo-controlled randomized double blinded study that appropriately blinded patients
- Both treatments were modeled to look and taste the same
- They appropriately chose a power of 90% and enrolled enough patients to achieve their power
- Examined a known marker (triglycerides) indicating exposure to the active drug, in both arms of the study. Since TG's were significantly decreased only in the O3-FA arm it increases the readers assurance that contamination was not an issue in the placebo group
- They used 3.3 grams of O3-FA/day which is correct because the dose for RA is 3-6 g/day.

LIMITATIONS:

- Larger than expected placebo effect was found (>50%) which could have led to poor results
- Compliance was not appropriately measured
- Researchers did not exclude patients who had prior hormone replacement therapy even though it's a risk factor for AI related joint stiffness and pain in hands and feet. In addition, they also failed to look at cessation of menstrual function which is also a risk factor for AI induced arthralgia
- The administration of the O3-FA was not mentioned. It is recommended that patients take the 3-6 g/day in divided doses for RA but the researchers did not tell us if the patients took it at once or not. In addition, the FDA maximum dose of non-prescription O3-FA is 3 grams/day and the study used more than the max dose.
- BPI-SF pain scale is a retrospective questionnaire that requires patients to rate pain over the past week and the degree in which it interfered with activities. In general, retrospective designs risk giving inaccurate results
- The placebo ingredients were not considered prior to the study and may have caused skewed results since the efficacy of Soybean and Corn Oil in reducing arthralgia pain has not been studied

CONCLUSION:

- Although the study showed no meaningful difference between groups, O3-FA treatment may be beneficial in actual practice and it certainly won't harm users.
    - AI's have proven to cause AI related arthralgia, and lower triglycerides (TG) and O3-FA's have proven efficacy in lowering TG's and in reducing pain and inflammation in RA
    - Current treatment options for AI arthralgia is stop the AI and most pain subsides (sometimes unrealistic option in BC), switch to Tamoxifen or stop taking estrogen inhibitors all together. If we could find a way to decrease the joint pain and stiffness enough so that patients could tolerate it and could continue the medication then I would consider the therapy a success and in this study O3-FA's were able to decrease the pain by 30-35% which is a starting place. The only harm associated with O3-FA's is possible diarrhea
- Future research:
    - Since the placebo contained ingredients that may have interfered with results, future research should use a placebo that doesn't contain any active ingredients
    - More research on the mechanism of AI associated arthralgia is necessary so that we may better understand how to treat the symptoms.

Reference: Hershman DL, Unger JM, Crew KD, et al. Randomized Multicenter Placebo-Controlled Trial of Omega-3 Fatty Acids for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain: SWOG S0927. J Clin Oncol. 2015;33:1910-1917.

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