



What Have We Learned from Clinical Trials on Sex Differences in SSc-ILD

The title of this abstract is the sex differences in severity and progression of interstitial lung disease and systemic sclerosis, what we have learned from clinical trials and it's from the lead author Elizabeth Volkmann from UCLA. In rheumatology, we're accustomed to conditions with sex and racial and ethnic disparities. Systemic sclerosis is well known to disproportionately afflict females more than males. However, males have been observed to have higher mortality rates. So the goal of what they're presenting is to compare treatment response outcomes in male and female participants from two randomized clinical trials for systemic sclerosis, scleroderma lung studies I and II, other studies and also whether sex differences exist in long-term mortality outcomes in these participants. So here are the results for the treatment responses in SLS I, the authors looked at the course of the FVC and those on placebo and those on cyclophosphamide by sex.

There was a trend for worsening of FVC in males in the placebo group, but no differences in the cyclophosphamide group. The cyclophosphamide arm in SLS II that I'll talk about now had a different outcome. In SLS II the authors looked at the course of the FVC in those on MMF and in those on cyclophosphamide by sex. There was no difference in the MMF group but unlike SLS I, the females improved compared to males in the cyclophosphamide group who worsened in the first 12 months. Now looking at mortality in SLS I, participants were followed up to 12 years and there was a trend towards improved survival in females. In SLS II, participants were followed up to eight years and females had significantly improved survival compared to males, even when you control for modified Rodnan skin score, age and baseline FVC. So the conclusions were that the two large randomized controlled studies demonstrated males had increased progression of ILD in the absence of treatment and worse long-term survival.

Some thoughts were that SLS I had a trend towards worsening FVC in males compared to females in the placebo group, but was not significant. This is a study that also had a trend but not significance towards improved survival in females. SLS II showed statistical improvement in survival in females compared to males, but did not have a study arm without treatment. Here the cyclophosphamide group showed significant improvement in females and worsened in males up to 12 months, but were not statistically different at 24 months. So how true are the differences between males and females? And are the differences in outcomes, particularly the time to death related to response differences between the groups? Undoubtedly there are environmental factors after they left a two year control part of the studies and went into the long-term follow-up. Things like adherence especially in smoking, but these were not evaluated in this result.

Another question is, were there racial differences considering some of the makeup of these different studies? Now these are outstanding questions that we'll have to continue to struggle with as clinicians, but these two large randomized clinical trials are a great springboard to look into these differences further. The results from these trials suggest some potential differences but I don't think the signal is strong enough nor are the designs of the studies from which these conclusions derived clear enough to indicate any change in management, other than maybe some heightened awareness of some potential



differences in sex. But in terms of actual application as to how we approach our patients, what we do and when we do them, I don't think it changes anything in terms of our management yet.