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Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012;366:1968-77.

Idiopathic Pulmonary Fibrosis (IPF) continues to be a devastating disease with no clinically significant treatment options. For years the treatment of IPF centered on a trial of prednisone followed by the addition of either cyclophosphamide or azathioprine as a 'lets see if this helps' approach. The 2011 ATS Consensus statement on IPF declared that the use of prednisone as monotherapy was not recommended. The consensus statement also yielded a weak recommendation for N-acetylcysteine (NAC) as monotherapy, and a weak recommendation of prednisone, azathioprine and NAC as combination therapy. This study is the first large multicenter, double-blind, placebo controlled trial looking at lung function in groups of patients treated with NAC monotherapy verses combination therapy (prednisone + azathioprine + NAC) versus placebo.

The study was performed throughout 25 centers from 2009-2011. Inclusion criteria were a diagnosis of IPF, age 35-85, FVC > 50% and DLCO > 30%. A total of 236 patients were included in the study and randomized into 3 groups...81 patients NAC monotherapy, 77 patients prednisone + azathioprine + NAC, and 78 patients placebo. The primary outcome was the change in FVC over a 60 week period. Secondary outcomes looked at were mortality rates, frequency of exacerbations, and disease progression.

The study was intended to proceed for duration of 60 weeks. Midpoint analysis at 30 weeks revealed the prednisone + azathioprine + NAC group had higher rates of respiratory and non-respiratory related death, hospitalizations, and exacerbations, Study data on NAC is unknown as the trial remains ongoing for Placebo verses NAC. First do no harm is used often in medicine and perhaps it should now be included into the IPF treatment algorithm. This study supports prior data that targeting this disease with anti-inflammatories and immune-modulators is not only ineffective but harmful. Our attempts at understanding and treating this disease remain futile and with the exception of lung transplantation.... ineffective. Although I am curious to see what if any benefit NAC will have against placebo, I am doubtful it will be significant. If NAC does prove to be beneficial, I would like to see a follow up study incorporating NAC in combination with esophageal reflux therapy in the treatment of IPF.

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