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Safety and Tolerability of Cyclophosphamide Versus Mycophenolate for Systemic Sclerosis-Related Interstitial Lung Disease

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc). Although cyclophosphamide (CYC) demonstrated beneficial treatment effects at one year on FVC and self-reported dyspnea (1), these benefits came at the expense of a high degree of adverse effects. Uncontrolled studies have demonstrated that mycophenolate (MMF) may improve SSc-ILD; however, no studies have directly compared outcomes of CYC and MMF in SSc-ILD. The present double-blind, randomized, placebo-controlled trial (RCT) compared the effects of CYC versus MMF in patients with SSc-ILD.

Methods: Between September 2009 and January 2013, 142 SSc-ILD patients from 14 US centers were randomized to receive MMF (titrated as tolerated to 3.0 g/day in divided doses) for 2 years or oral CYC (titrated as tolerated to 2 mg/kg daily) for 1 year followed by 1 year on placebo. Inclusion criteria were age ≥18 years, duration of disease ≤7 years from onset of the first non-Raynaud's SSc symptom, FVC 40-80% predicted, DLCO ≥40% predicted (or 30-39% predicted if no evidence of pulmonary hypertension on echocardiogram and/or right heart catheterization), and evidence of *any* ground glass opacity on HRCT. The primary endpoint was treatment responsiveness as measured by the course of the FVC% predicted over 24-months.

Results: Among 142 participants (Mean [SD] age 52.3 [9.7] years), 74% were female and 59% had diffuse cutaneous involvement. The mean disease duration was 2.6 [1.8] years. Baseline pulmonary function was as follows (All Mean [SD]% predicted): FVC 66.5 [9.1]; TLC 65.9 [10.9];

DLCO 54.0 [12.7]. Baseline quantitative lung fibrosis (QLF) scores were 32.5 [23.8] and 8.6 [6.8], for the zone of maximum involvement and whole lung, respectively. By 24 months, approximately half (49%) of the participants assigned to CYC (N=73) went off drug, compared with 29% of participants assigned to MMF (N=69). A greater proportion of participants assigned to MMF reached the required dosage compared with CYC, and the time to reach the maximum targeted dose was significantly longer in the CYC arm (152 days) compared with the MMF arm (92 days). Participants assigned to CYC experienced more serious adverse events (SAEs) considered to be drug-related by a morbidity and mortality committee compared with patients assigned to MMF (22% versus 7%, respectively), although the majority of SAEs were deemed to be related to underlying ILD (Table 1). During the study period, there were 11 deaths (15%) in the CYC group and 5 deaths (7%) in the MMF group.

Conclusion: The present findings demonstrate that treatment with MMF is associated with fewer SAEs deemed to be drug-related and fewer deaths compared with treatment with CYC in patients with SSc-ILD. Moreover, MMF appears to be better tolerated than CYC.

References:

1. Tashkin DP, et al. NEJM 2006;354:2655-2666.

Table 1. Summary of serious adverse events (SAEs) for participants assigned to CYC (N=73) versus MMF (N=69).

	CYC	MMF
Total Number of SAEs	36	42
SAEs due to drug (%)	22.2%	7.1%
SAEs due to underlying disease (%)	44.4%	38.1%
SAEs due to other causes (%)	31.6%	52.4%
SAE not yet reviewed (%)	2.8%	2.4%

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