Results of the Avonex Combination Trial (ACT)

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OBJECTIVE: ACT was a multicenter investigator-run safety and efficacy trial of interferon beta-1a (IFN-1a, Avonex) combined with methotrexate (MTX), intravenous methylprednisolone (IVMP) or both for relapsing-remitting multiple sclerosis (RRMS) patients with active disease on IFN-1a monotherapy.

BACKGROUND: Current RRMS therapies are partially effective. Combination therapies are useful for other disorders. Preliminary data support safety and benefit of MTX or IVMP combined with IFN in MS. DESIGN/METHODS: Eligibility criteria included RRMS, EDSS 0-5.0 and active disease (1 relapse or gadolinium enhancing MRI lesion) in the prior year on IFN-1a therapy. Subjects were randomized to adjunctive weekly placebo or MTX 20 mg PO, each with or without IVMP 1000 mg/d 3d every other month, and followed 12 months. ACT was governed by an investigator Steering Committee with input from independent Advisory and Data Safety Monitoring Committees, and managed by the Cleveland Clinic MS Academic Coordinating Center.

RESULTS: The four treatment groups (n=313 total) had similar baseline demographic, clinical and MRI characteristics. MTX-IVMP-IFN-1a combinations were safe and well-tolerated. Last-observation-carried-forward mean-imputed data showed favorable, though not statistically significant, trends in multiple clinical and MRI outcomes, with least evidence of disease activity usually in the three-drug combination. New or enlarged T2 lesions, the primary outcome, averaged 1.53/patient overall with upper-count category odds ratios (95% CI) in a main-effects proportional odds model MTX 0.90 (0.59-1.36) and IVMP 0.74 (0.48-1.13). Relapses averaged 0.40/patient-year overall with rate ratios in a main-effects negative binomial regression model MTX 0.77 (0.51-1.16) and IVMP 0.70 (0.46-1.05). Baseline to last observation T2 volume percent increase was reduced by IVMP ($p=0.038$) but not significantly by MTX.

CONCLUSIONS/RELEVANCE: Initial analyses of ACT showed trends favoring the combination therapy regimens. Further pre-planned analyses, including multiple imputation analyses, are in progress. ACT provides an innovative model for academic-industry collaborative MS research.