Rescuing Standard Analyses of Immunosuppressive Rescue Therapy in Randomized Controlled Trials: Alternative Approaches in a Sclerosis in a Clinical Trial

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BACKGROUND

• Treatment with CTLA4ig, abacetherapy (ABA), and in early diffuse cutaneous systemic sclerosis (dcSSc; the Phase 2 ASSET trial) showed evidence of improvements in modified Rodnan skin score (mRSS) and secondary outcome measures at month 12 (2018 ACR abstract # 900).

• This randomized placebo-controlled trial used the gold standard for providing the highest-quality evidence of treatment efficacy; however, requiring participants with early dcSSc to take long-term placebo raises feasibility and ethical concerns.

• Many studies, including ASSET, allow rescue therapy when a participant’s condition worsens.

• Statistically, adjusting for rescue therapy to derive appropriate conclusions about treatment efficacy is complicated because it is a post-randomization variable.

• We applied several analytic approaches to address rescue therapy in the primary endpoint in ASSET – change from baseline to month 12 in mRSS.

METHODS

• ASSET was an investigator-initiated, multicenter double-blind, randomized placebo-controlled trial.

• Eligible subjects were randomized in a 1:1 ratio to 12 mg ABA or matching placebo, stratified by duration of dcSSc (≥18 vs. >18 to ≤36 months).

• After 6 mo of treatment, investigators were given a choice to add rescue therapy for a worsening skin disease (>5 units worsening of mRSS) or worsening ILD (absolute decline in FVC’s predicted by ≥10% or absolute decline in DLCO predicted by ≥5).

• If subject worsened at 3 mo, investigators could begin escape therapy, but were to stop study medication.

• The primary analysis for treatment comparisons was based on the ITT principle for inclusion of participants, but we eliminated data after the onset of rescue therapy. (Table 2, method #1)

• Linear mixed models were used to assess treatment differences in change in mRSS scores. (Table 2, method #2)

• Alternative approaches included 1) adjusting for a post-randomization variable (Table 2, method #3), 2) including rescue therapy as a covariate (Table 2, method #1), and 3) analyzing data until the onset of rescue therapy (Table 2, method #2).

RESULTS

• 88 subjects (44 ABA, 44 PBO) were randomized (34 (77%) of ABA subjects completed 12 months on study: 35 (80%) of PBO subjects completed 12 months on study.

• There are multiple approaches in the literature for handling rescue therapy results.

• The National Academy of Sciences panel on handling missing data in clinical trials emphasized limiting missing data in the design of clinical trials [1]. One of their 8 ideas included ‘allow the use of rescue medications that are designated as components of a treatment regimen in the study protocol.’

• Recent FDA and EMA guidelines [2, 3] emphasize selecting the correct estimand -- the right quantity to be estimated -- at the design stage to address the right question regarding treatment differences when non-adoherence and missingness occur study conduct.

• There are multiple approaches in the literature addressing the difficulties with analyses and interpretation after rescue therapy.

• In our study, there was differential use of rescue therapy by treatment, but several simple approaches to handling rescue therapy results in comparable conclusions, providing confidence in our primary analytic approach.

• More sophisticated analytic methods, such as jointly modeling the primary endpoint and the probability of rescue therapy may be useful.

CONCLUSIONS

• Statistically, adjusting for rescue therapy to derive appropriate conclusions about treatment efficacy is complicated because it is a post-randomization variable.

• Linear mixed models were used to assess treatment differences in change in mRSS scores.

• Alternative approaches included 1) adjusting for a post-randomization variable (Table 2, method #3), 2) including rescue therapy as a covariate (Table 2, method #1), and 3) analyzing data until the onset of rescue therapy (Table 2, method #2).

• The largest mean treatment difference occurred after eliminating values after start of rescue therapy (method #1)

• The smallest mean treatment difference occurred by eliminating values before start of rescue therapy.

• The mean treatment difference increased when all values were included, as might be expected with twice as many placebo participants starting rescue therapy (method #2)

• Censoring values and incorporating rescue therapy as a covariate resulted in an intermediate treatment estimate (method #3)

• No statistically significant treatment differences were observed from any model.

REFERENCES


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